Faculty of Medicine, University of Helsinki
Department of Anesthesiology, Intensive Care and Pain Medicine
Helsinki University Hospital, Helsinki Finland

POSTOPERATIVE PAIN

RISK FACTORS, PREDICTIVE METHODS, AND PAIN MANAGEMENT IN SPECIFIC PATIENT GROUPS

Hanna von Plato

ACADEMIC DISSERTATION

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SUPERVISED BY

Docent Katri Hamunen, M.D.,Ph.D.
Department of Anesthesiology, Intensive Care and Pain Medicine
Helsinki University Hospital and University of Helsinki
Helsinki, Finland

Docent Vesa Kontinen, M.D.,Ph.D.
Department of Anesthesiology, Intensive Care and Pain Medicine
Helsinki University Hospital and University of Helsinki
Helsinki, Finland

REVIEWED BY

Docent Minnaliisa Niskanen, M.D.Ph.D.
Department of Anesthesiology and Intensive Care
Kuopio University Hospital and University of Eastern Finland
Kuopio, Finland

Associate professor Teijo Saari, M.D.,Ph.D.
Department of Anesthesiology, Intensive Care and Pain Medicine
Turku University Hospital and University of Turku, Turku, Finland

OPPONENT

Docent Maija Kalliomäki, M.D.Ph.D.
Department of Anesthesiology
Tampere University Hospital and University of Tampere,
Tampere, Finland

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To Venny, Vesta and Ville

ABSTRACT

Despite of many efforts, acute postoperative pain is still a major problem. Approximately half of surgical patients worldwide report clinically significant pain after surgical procedures. Although the intensity of postoperative pain depends somewhat on the procedure, marked variation exists in pain intensity between individual patients.

Our main objective was to evaluate the efficacy and safety of various analgesic techniques and in particular to evaluate the efficacy and safety of a continuous perineural local anesthetic infusion combined to a wound infusion for the treatment of postoperative pain after above knee amputation. In addition we investigated the demographic and individual psychological risk factors for postoperative pain, including anxiety, the expectation of pain, fear of pain, and the patient's need for more information about postoperative pain and pain management and its correlation with acute postoperative pain in a range of elective surgical procedures. Finally, we investigated a short five-item questionnaire in evaluating the risk of postoperative pain in day-case cholecystectomy, and to assess the efficacy and safety of targeted single-dose preoperative pregabalin in a high-risk group of cholecystectomy patients.

Based on our systematic review of the literature to date (study I), there seems to be minimal data that supports current clinical practice on pain management in acute pain after amputation. Epidural analgesia may be effective, but current treatment regimens are too heterogenous for firm evaluation and data quality is low. Our results also indicate that continuous perineural sciatic infusion probably decreases acute pain levels after major amputation, but prior evidence is scarce.

In the second part of the thesis, a combination of a continuous sciatic perineural infusion and a wound infusion of a local anesthetic was shown to diminish average stump pain and opioid consumption after above knee amputation compared to placebo during the first 5 postoperative days (study II). There was no effect on the manifestation of postoperative chronic pain, defined as pain lasting for 3 months or longer. No difference in the number of adverse effects was seen.

In the third part of this thesis, the role of demographic and psychological predictive factors, including the expectation of pain, younger age, chronic pain, and prior use

of opioids, was shown to affect postoperative pain levels in a mixed surgical population (study III). Among other individual risk factors, there was a correlation between high expectation of pain and the resolution of acute pain during the first postoperative days.

In the fourth part of the thesis, the preoperative question about anxiety (rated on a scale of 0-10) had a positive correlation with postoperative pain (study IV). Preoperative pregabalin 150 mg administered targeted to cholecystectomy patients with many risk factors for postoperative pain did not decrease postoperative pain intensity compared with placebo.

The results of this thesis demonstrate that acute postoperative pain management after amputation has been inadequately studied (study I). Continuous perineural infusion (CPI) of a local anesthetic combined to a wound infusion seems to be beneficial after thigh amputation in terms of opioid consumption on the first postoperative day, and postoperative pain during first five postoperative days (study II). In a wide range of elective operations, chronic pain, the expectation of pain, and inadequate preoperative information on postoperative pain are associated with pain (study III). Preoperative pregabalin 150 mg administered to cholecystectomy patients with many risk factors for postoperative pain did not decrease postoperative pain intensity compared to placebo. The simple preoperative question on anxiety had a positive correlation with postoperative pain (study IV).

TIIVISTELMÄ

Leikkauksen jälkeisen kivun intensiteetti on leikkaustyypin lisäksi riippuvainen potilaskohtaisista yksilöllisistä tekijöistä. Arvellaan, että maailmanlaajuisesti jopa noin puolet potilaista kokee merkittävää kipua leikkauksen jälkeen.

Yksi tämän väitöskirjatutkimuksen tavoitteista oli selvittää eri kivunhoitomenetelmien tehoa ja turvallisuutta amputaatioiden jälkeisen kivun hoidossa, ja tutkia jatkuvan iskiashermotuppipuudutuksen ja haavapuudutuksen yhdistelmän tehoa ja turvallisuutta akuutin leikkauksen jälkeisen kivun hoidossa reisiamputaation läpikäyneillä potilailla joilla on valtimokovettumatatauti. Toinen tavoite oli tutkia leikkauksen jälkeisiä yksilöllisiä riskitekijöitä ja niiden vaikutusta koetun kivun voimakkuuteen elektiivisillä leikkauspotilailla. Tutkimme myös yksinkertaisen viiden kohdan kyselyn kykyä erotella riskitekijöiden perusteella elektiiviseen päiväkirurgiseen tähystykselliseen sappileikkaukseen tulevista potilaista etukäteen ne, joilla on korkeampi riski vaikealle leikkauksen jälkeiselle kivulle, ja mahdollisuutta kohdentaa heille tehokkaampaa kivun hoitoa jo ennen leikkausta. Tutkimme leikkausta ennen kerta-annoksena annostellun pregabaliinin tehoa kohdennetusti niille potilaille joilla oli paljon riskitekijöitä kivulle.

Systemaattinen katsaus osoitti, että akuutin amputaatiokivun hoitoa käsitteleviä tutkimuksia on vain vähän ja tutkittua tieteellisessä mielessä laadukasta tietoa johon hoitokäytäntöjä voisi perustaa on aiheesta rajallisesti. Epiduraalipuudutus näyttäisi mahdollisesti olevan tehokas mutta tutkimukset sen tehosta ovat hyvin heterogeenisiä ja laadullisesti huonoja. Jatkuva hermopunospuudutus iskiashermotuppeen mahdollisesti vähentää akuuttia kipua alaraaja-amputaation jälkeen, mutta näyttö tästä on vähäistä.

Tekemämme vertailevan tutkimuksen perusteella jatkuvan iskiashermotuppipuudutuksen ja haavapuudutuksen yhdistelmä vähentää kipua ja ensimmäisen leikkauksenjälkeisen päivän opioidin kulutusta reisiamputaation jälkeen, verrattuna lumelääkkeeseen. Se ei aiheuta sivuvaikutuksia iäkkäille potilaille. Tutkimuksemme perusteella sillä ei näyttäisi olevan vaikutusta krooniseen kipuun amputaation jälkeen.

Yksilölliset tekijät kuten nuorempi ikä, odotus voimakkaasta kivusta, krooninen kipu ja opioidi kipulääkkeiden edeltävä käyttö vaikuttavat leikkauksen jälkeisen kivun

voimakkuuteen leikkaukseen katsomatta. Myös kokemus leikkausta edeltävästä riittämättömästä informaatiosta koskien kipua ja kivun hoitoa on yhteydessä leikkauksen jälkeiseen kipuun. Leikkausta edeltävä odotus kovasta kivusta on yhteydessä leikkauksen jälkeiseen hitaaseen kivun lieventymiseen.
Päiväkirurgisilla sappipotilailla leikkauksen jälkeisen kivun ennustaminen viiden yksinkertaisen kysymyksen avulla ei tutkimuksessamme onnistunut odotetulla tavalla. Ainoastaan potilaan oma arvio ahdistuksesta asteikolla 0-10 oli yhteydessä leikkauksen jälkeiseen kipuun. Leikkausta ennen kerta-annoksena annettu 150 mg annos pregabaliinia kohdennetusti niille potilaille joilla oli paljon riskitekijöitä, ei vähentänyt leikkauksen jälkeisen kivun intesiteettiä tai opioidin kulutusta verrattuna lumelääkkeeseen.
Tämän väitöskirjatutkimuksen tulokset osoittavat, että akuutin kivun hoitoa amputaatiopotilailla ei ole tutkittu paljoakaan. Vertailevassa tutkimuksessamme jatkuva iskiashermotuppeen annosteltava puuduteinfuusio yhdistettynä haavapuudutukseen osoittautui hyödylliseksi, akuutin kivun voimakkuus ja opioidin kulutus ensimmäisen päivän aikana leikkauksen jälkeen vähenivät. Tutkimuksemme perusteella näyttää myöskin siltä, että elektiivisillä kirurgisilla potilailla nuorempi ikä, krooninen kipu, odotus kivun intensiteetistä ja kokemus riittämättömästä informaatiosta ennen leikkausta koskien kipua ja kivun hoitoa ovat yhteydessä leikkauksen jälkeiseen kipuun. Riittämätön informaatio ennen leikkausta ja odotus korkeasta leikkauksen jälkeisen kivun intensiteetistä ennustavat korkeampaa kipua ja kivun hitaampaa lievittymistä leikkauspotilailla, ja tämän huomioiminen leikkausta edeltävästi parantaisi kivun hoidon onnistumisen mahdollisuutta. Elektiivisillä päiväkirurgisilla sappileikkauspotilailla leikkauksen jälkeisen kivun ennustaminen lyhyen riskitekijäkyselyn avulla osoittautui vaikeaksi, eikä ennen leikkausta kohdennetusti riskipotilaille annosteltu pregabaliini vähentänyt leikkauskipua tai opioidin kulutusta.

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ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
AKA	Above-knee amputation
APAIS	Amsterdam Preoperative Anxiety and Information Scale
APS	Acute pain service
ASA	American Association of Anesthesiologists status
B-MEPS	Brief measure of emotional preoperative stress index
BKA	Below-knee amputation
BMI	Body mass index
CPI	Continuous perineural infusion
DN2	Self-administered Neuropathic Pain Diagnostic Questionnaire
DN4	Neuropathic Pain Diagnostic Questionnaire
DPMS	Descending pain modulatory system
ECF	Extracellular fluid
FSPQ	Future Self-perception Questionnaire
IASP	International Association for the Study of Pain
ICF	Intracellular fluid
IL	Interleukin
i.m.	Intramuscular
i.v.	Intravenous
LA	Local anesthetic
LCC	Laparoscopic cholecystectomy
LOT	Life Orientation Test
MADRS	Montgomery-Åsberg Depression Rating Scale
MEP	Motion-evoked pain
NMDA	N-methyl-D-aspartate
NSAID	Nonsteroidal anti-inflammatory drug
NRS	Numerical rating scale
PAINAD	Pain Assessment in Advanced Dementia Scale
PAR	Pain at rest
PCS	Pain Catastrophizing Scale

RCT	Randomized controlled trial
RSB	Rectus sheet block
STAI	The Spielberger State-Trait Anxiety Inventory
STAI-S-T	Reduced version of the State-Trait Anxiety Inventory
SQR-20	WHO Self-reporting Questionnaire
TAP	Transversus abdominis plane block
TIVA	Total intravenous anesthesia
TNF	Tumor necrosis factor
VAS	Visual analogue scale
VRS	Verbal rating scale
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

The present thesis is based on the following original publications, referred to in the text by their Roman numerals.

I **von Plato H**, Kontinen V, Hamunen K. Efficacy and safety of epidural, continuous perineural infusion and adjuvant analgesics for acute postoperative pain after major limb amputation – a systematic review. *Scand J Pain. 2018;18:3.17.*

II **von Plato H**, Peltoniemi M, Kauhanen P, Löyttyniemi E, Hamunen K, Kontinen V. Combination of perineural and wound infusion after above knee amputation: A randomized, controlled multicenter study. Acta Anaesthesiol Scand. 2019;63:1406-1412.

III **von Plato H**, Löyttyniemi E, Kontinen V, Hamunen K. Correlates of individual preoperative factors and expectations with acute postoperative pain. *Submitted.*

IV **von Plato H**, Mattila K, Poikola S, Löyttyniemi E, Hamunen K, Kontinen V. Risk-based targeting of adjuvant pregabalin treatment in laparoscopic cholecystectomy: A randomized, controlled trial. *Scand J Pain. 2019;19:309-317.*

1 INTRODUCTION

According to recent studies, approximately 40% to 60% of patients going through surgical procedures experience significant acute postoperative pain (Chou et al. 2016, Vrancken et al. 2018, Gan et al. 2014, Zaslansky et al. 2015, Pogatzki-Zahn et al. 2017). Postoperative pain has many negative consequences. By decelerating recovery and rehabilitation, postoperative pain enhances postoperative morbidity and complications. Pain may prolong hospital stay and increase hospital costs (Brennan et al. 2007, Taylor et al. 2013, Gaskin et al. 2012, Macrae et al. 2008). Postoperative acute pain may be a risk factor for chronic pain and may cause long-term working disability (Kehlet et al. 2006, Chou et al. 2016, Althaus et al. 2014, Wu et al. 2004, Apfelbaum et al. 2003, Sommer et al. 2008, Lorentzen et al. 2012). Although the intensity of postoperative pain depends on surgery-related factors, individual factors such as preoperative pain, demographics, and psychological factors also contribute to the pain experience (Yang et al. 2019, Nielsen et al. 2009, Ip et al. 2009, Sobol-Kwapinska et al. 2016, Gerbershagen et al. 2014).

Thigh amputation is a surgical procedure that results in major tissue damage of bone, soft tissue, and nerves. Postoperative pain is often severe despite use of multimodal analgesia, and as preoperative pain caused by ischemia is a common cause for amputation, chronic postoperative pain is often evident. Patient comorbidities, age, and prior medications decrease the spectrum of analgesic methods available and increase the side effects of opioids. One way of improving the postoperative pain management in this challenging patient group is a continuous postoperative ischiatic perineural infusion.

Although procedure-specific postoperative pain management guidelines have improved the quality of treatment, an important aspect of pain management is overlooked. The traditional means of investigating postoperative pain management is procedure specific, even though there is growing evidence of the individual factors that contribute to postoperative pain. For example, when treating patients according to procedure-specific guidelines, most patients achieve good pain relief but there is nevertheless a considerable group of patients who suffer from severe postoperative pain.

The individual variation of postoperative pain between patients undergoing through surgical procedures and the individual factors leading to this variation are not considered if only procedure-specific pain management guidelines are followed when planning postoperative pain treatment. Postoperative pain after laparoscopic cholecystectomy is often treated according to procedure-specific guidelines that rely on randomized controlled trials (RCT). Despite these guidelines, there is a group of patients who suffer from severe acute postoperative pain. Targeting postoperative pain management involves preoperatively screening the patients for individual demographic and psychological risk factors for pain, and planning postoperative pain management according to the patient's needs. Preoperative evaluation for postoperative pain risk may enable the use of adjuvant preoperative analgesics prior to surgery in high-risk patients.

The first objective of this thesis was to investigate the existing scientific evidence concerning acute pain management after major amputations. Furthermore, we examined the possibility of modulating acute postoperative pain in a clinical setting with a local anesthetic perineural infusion after thigh amputation. In addition, we examined the intensity of acute postoperative pain in a wide range of surgical procedures and the contributing individual risk factors. Finally, we examined the possibility of targeting an adjuvant preoperative medication based on individual risk factors in laparoscopic cholecystectomy.

2 REVIEW OF THE LITERATURE

2.1 ACUTE POSTOPERATIVE PAIN

2.1.1 EPIDEMIOLOGY

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (IASP 2014). Acute pain is defined as pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease (Ready et al. 1992). Acute pain is usually defined as pain lasting for less than 3 months, but classification based on time has limitations if the underlying pathophysiology is not considered (Schug et al. 2015).

Although acute postoperative pain and pain management has been studied for decades, acute postoperative pain is common and the many challenges in management remain. According to a recent study, of the 1014 elective surgical patients included going through various procedures, 55% experienced moderate to severe pain (NRS 4-10) on the first postoperative day. The study concluded that the incidence of severe postoperative pain has not improved in recent decades (Boekel et al. 2019).

As Gan et al. suggested, 75% of surgical patients experienced moderate or severe acute pain after surgery and 74% experienced moderate or severe pain after discharge at home. The worst preoperative concern was postoperative pain and nearly half of the patients preoperatively reported high or very high anxiety concerning postoperative pain. Postoperatively, 80% of patients experienced adverse effects of analgesics and 39% still reported moderate-to-severe pain after the first postoperative analgesic dose (Gan et al. 2013).

Another study revealed that 80% of patients experienced pain after surgery and 86% of these patients had moderate or severe pain (Apfelbaum et al. 2003).

Similar findings were reported in a German study, where 41% of patients experienced moderate or severe postoperative pain on the day of surgery, 31% on the first postoperative day, and 19% on the second postoperative day. Of the patients going through abdominal surgery, 30% to 55% experienced moderate-to-severe pain on the day of surgery and on the first postoperative day. Approximately 30% to 64%

of the patients going through spinal surgery experienced moderate-to-severe pain on 4 postoperative days (Sommer et al. 2008).
In a study on day-case surgery, 26% of patients had moderate-to-severe pain on the day of surgery. Abdominal operations, orthopedic operations, operations of ear, nose, and throat, and plastic surgery of the breast were the most painful in day-case surgery during the first 2 postoperative days (Gramke et al. 2007).

2.1.2 PATHOPHYSIOLOGY OF POSTOPERATIVE PAIN

Surgery and postoperative pain cause a complex metabolic, hemodynamic, humoral, immune, and somatosensory response (Schug et al. 2015). Certain triggers, predisposing factors, and mediating factors contribute to the pain response, as described in detail in figure 1. (Blackburn et al. 2011, Prabhakar et al. 2014, Desborough et al. 2000, Schug et al. 2015). Of these factors, it is somewhat difficult to separate which are caused by surgery and which are a consequence of acute pain (Boekel at al. 2019). Postoperative pain is a combination of nociceptive, inflammatory, visceral, and neuropathic pain; these features depend on the procedure and on individual factors.

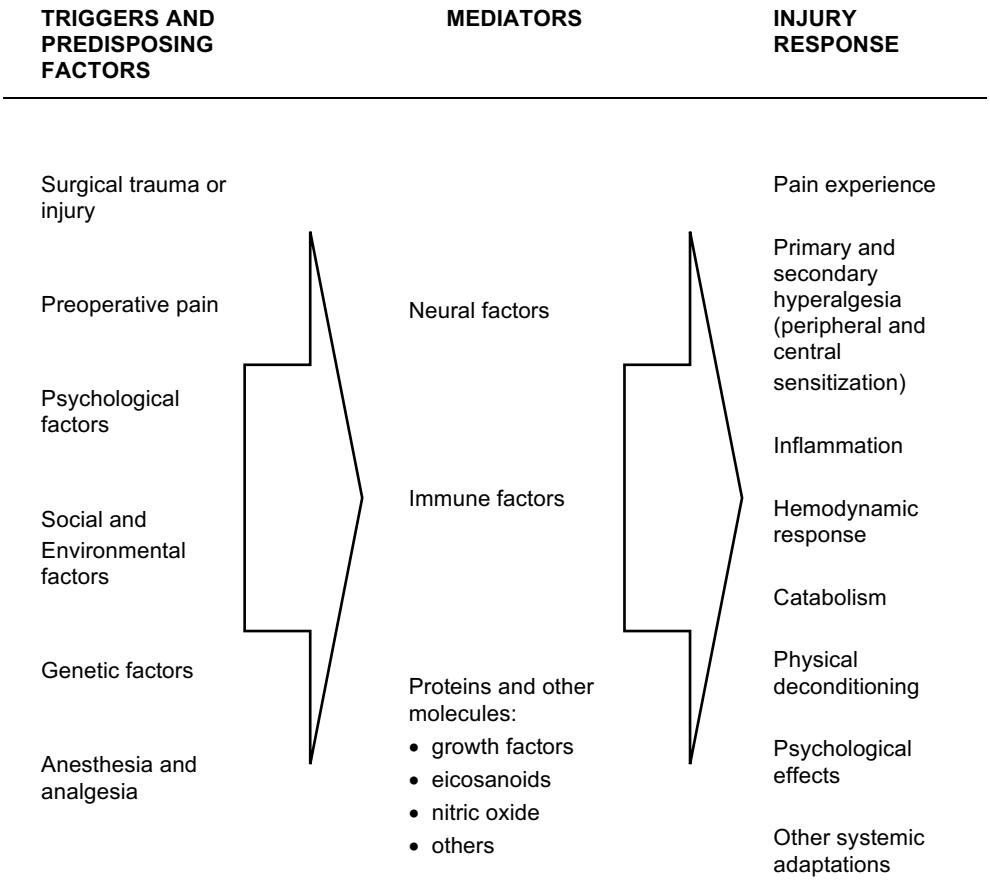

Figure 1. The pain response, adapted from Schug et al. 2015.

Surgery triggers a complex cascade of consequences and an injury response that have metabolic, immunological, and endocrine features (Schug et al. 2015). These are described in detail in Table 1.

Table 1. Metabolic, immunological and endocrine responses to injury, adapted from Schug et al. 2015.

Endocrine	catabolic hormones ↑	ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagon ↑
	anabolic hormones ↓	insulin, testosterone ↓
Immune	mitochondrial initiation	alarmins
	proinflammatory followed by compensatory response	IL-1, TNFα, IL-6, IL-4, IL-8, IL-10 chemokines
Metabolic		
• carbohydrate	hyperglycemia, glucose intolerance, insulin resistance	glycogenolysis, gluconeogenesis, cortisol, glucagon, growth hormone, adrenaline, free fatty acids ↑ insulin secretion and activation ↓
• protein	muscle protein catabolism synthesis of acute phase proteins ↑	cortisol, adrenaline, glucagon, IL-1, IL-6, TNF ↑
• lipid	lipolysis and oxidation ↑	catecholamines, cortisol, glucagon, growth hormone ↑
Water and electrolyte flux	retention of water and sodium excretion of potassium ↑ functional ECF → ICF ↓	catecholamines, aldosterone, ADH, cortisol, angiotensin II, prostaglandins ↑

2.1.3 TRANSMISSION, MODULATION, AND THE PERCEPTION OF PAIN

Nociception, that can be described as the ability of the somatosensory system to detect potentially tissue-damaging stimuli and consists of a cascade of functions in the peripheral and central nervous system. The detection of noxious stimuli by peripheral sensory nerve endings (nociceptors) is followed by the transduction of noxious stimuli into electrical activation, and the conduction of the signals in peripheral sensory nerves to the central nervous system. Transmission occurs when a nociceptive signal reaches the presynaptic terminal in the dorsal horn of the spinal cord. Modulation of the nociceptive transmission is an adaptive process that involves both excitatory and inhibitory mechanisms (Schug et al. 2015).
Sensitization is a characteristic of nociceptors. Tissue injury due to surgery causes the release of chemical mediators that resulting in peripheral sensitization at the level of the primary afferent fibers. Peripheral sensitization is a contributor to pain and primary hyperalgesia after surgery.

Central sensitization is characterized by increased responsiveness of nociceptive neurons in the central nervous system. Secondary hyperalgesia is believed to be mainly due to central sensitization and it is suggested to be related with persistent postoperative pain. The descending pain modulatory system (DPMS) is a brainstem-subcortical-cortical network that modulates nociceptive processing at the dorsal horn in a strengthening or dampening manner to control the nociceptive input into the brain.

Multiple factors contribute to the perception of pain. Pain perception can be defined as an interpretation of the nociceptive input influenced by pathological, emotional, genetic, and cognitive factors (Tracey et al. 2008). In the central nervous system, an extensive network known as the pain matrix is recruited. This matrix is modified by genetics, environment, mood, and the injury causing pain. The pain matrix can be thought of as having lateral, secondary somatosensory, thalamic, posterior, insula, anterior cingulate cortex, and prefrontal cortex neuroanatomical components. However, the pain matrix is not a defined entity because of the factors that influence pain perception (such as cognition, mood, and injury) play a role in the activation.

The genetics of acute pain have been studied, for example in terms of different genetic variants that modulate nociception and associate with pain sensitivity and determine drug metabolism and drug response. Studies are beginning to link genetic influences on human nociceptive processing with physical processes in the central nervous system (Zubieta et al. 2003). As experimental methods develop, the contribution of genomics to pain may be more systematically studied with the aim of targeting distinct molecular cascades. It is possible that targeted approaches coupled with effective patient phenotyping would enable truly personalized care in the future. Genetic linkage, next-generation sequencing and other omics have contributed significantly to understanding heritability and associations between genetic loci and pain conditions. The data suggest multiple genetic mechanisms in pain (Bullock et al. 2019).

2.1.4 ASSESSING ACUTE POSTOPERATIVE PAIN

Adequate assessment of pain with validated pain scales is essential for good pain management.

Postoperative pain can in most cases be measured with self-reported pain scales. Commonly used unidimensional pain scales include the 11-point numerical rating scale (NRS; from no pain [0] to worst pain imaginable [10]), the Visual Analogue Scale (VAS; from no pain [0] to worst pain imaginable [10 or 100]), and the five- or four-point Verbal Rating Scale (VRS). According to a review article on 54 studies of different pain measurement scales, the NRS is applicable for unidimensional assessment of postoperative pain in most settings (Hjermstad et al. 2011). In this

study, when compared with VAS and VRS, the NRS had better compliance in 15 of 19 studies that reported it. Due to higher compliance, better responsiveness, and ease of use, NRS was the recommended assessment method in 11 studies. However, as stated in another study, the pain assessment method should be suitable for the patient considered, such as those with possible cognitive impairment such as dementia (Breivik et al. 2008). In the elderly, it has been suggested that the VRS is applicable and easy to use even if dementia is present (Pesonen et al. 2009).
As immobilization is a known risk factor for complications and adequate pain relief aims restore early mobilization to reduce the risk of cardiopulmonary and thromboembolic postoperative complications, pain assessments should include measuring pain at rest (PAR) and movement-evoked pain (MEP) (Breivik et al. 2008). According to a review of MEP and PAR in trials, only 39% of trials reported MEP. Trials that measured MEP and PAR stated that MEP is significantly more intense in the first 3 postoperative days. It is recommended that MEP is included as a pain outcome in every trial investigating postoperative pain and in postsurgical trials in general (Srikandarajah et al. 2011). When assessing acute pain, a threshold for pain treatment should be used. In a study of 435 surgical patients, this threshold was determined on a four-item questionnaire. Patients preoperatively estimated their tolerable postoperative pain intensity. Twenty-four hours after the operation, patients indicated if they would have preferred more analgesics and reported satisfaction with analgesia. Pain intensities were also analyzed in relation to movement, breathing, sleeping, and ability to move. The study indicated pain categories of NRS 0 to 2 as mild, 3 to 4 as moderate, and 5 to 10 as severe pain (Gerbershagen et al. 2011).

2.2 ACUTE PAIN AFTER AMPUTATION

2.2.1 EPIDEMIOLOGY

In 2018, 725 above knee amputations (AKA) and 314 below knee amputations (BKA) were performed in Finland (National Institute for Health and Welfare, 2019). Peripheral vascular disease is the indication for major amputations in approximately 80% of the patients and usually affects the lower limbs (Dillingham et al. 2002). There is a minor proportion of amputations performed in young patients due to combat- and landmine-related injuries and injuries to civilians in war zones. In the United States, approximately 185 000 upper- or lower-limb amputations are performed annually (Owings et al. 1998). Despite of the development of vascular surgery, the amount of amputations is growing due to aging of the population. Most patients suffer from pain derived from ischemia preoperatively, and in many cases pain is one reason for amputation (Hsu et al. 2013). Patients with difficult diabetic neuropathy are an exception in this population. The neuropathy may cause a situation

where the limb to be amputated is not painful despite ischemia and after surgery the pain levels of these patients may be very low. This is something that is rarely considered in the studies that investigate acute pain after amputation and can be a source of bias.

Postamputation pain has two distinct manifestations. Stump pain or residual limb pain is experienced in the remaining body part. Phantom pain is pain that refers to the missing limb. A phantom sensation is a nonpainful perception of the missing limb. Stump pain is common in the acute phase, is often severe, and usually diminishes with healing of the surgical site (Buch et al. 2019). Phantom limb pain is very common postoperatively and can be severe and disabling. The incidence of phantom limb pain differs between studies and is approximately 60% to 80% (Buch et al. 2019, Hsu et al. 2013, Ephraim et al. 2005, Alviar et al. 2011). Acute phantom limb pain is present in approximately 72% of patients during the first week after amputation (Jensen et al. 1985). Approximately 75% of phantom limb pain develops during the first postoperative days, but late onset of phantom limb pain is possible (Hsu et al. 2013).

The incidence of phantom limb pain has been studied in a review that offers explanations for the differences in incidence between studies. The review stated that incidences vary depending on whether the study is retrospective, if it clearly distinguished phantom limb pain from residual limb pain and phantom limb sensation, if the study population consisted of patients seeking treatment for pain or not, and if the study involved researchers independent of treatment teams (Halbert et al. 2002). In this review of 375 patients in 12 studies, three trials revealed that 56% to 82% of the patients experienced phantom limb pain in the acute phase at day 7 after amputation. The review was limited by the low quality of the included trials.

2.2.2 RISK FACTORS FOR PAIN AFTER AMPUTATION

Postoperative pain after amputation is often severe due to the evident major trauma of skin, muscle, bone, and nerves. The degree of preoperative pain has an effect on the pain experienced postoperatively (Nikolajsen et al. 1997, Katz et al. 1997, Jensen et al. 1983, Jensen et al. 1985). Psychosocial factors also seem to affect postoperative pain (Halbert et al. 2002).

It was previously assumed that effective preoperative pain management preferably with epidural analgesia would affect postoperative pain after amputation and especially acute and persistent phantom limb pain. This preemptive pain management was first studied in a prospective trial of 25 patients, where 11 patients received a lumbar epidural blockade 3 days before the operation and 14 patients were treated with conventional analgesics. After 6 months, the incidence of phantom pain was significantly lower in 11 patients in the epidural group than in the 14 patients in

the control group. After 12 months there was no significant difference in pain between the groups. The trial was not blinded as randomization was performed according to patient year of birth. Only patients with preoperative pain were included in this trial (Bach et al. 1983). Another study confirmed these results (Jahangiri et al. 1994). These studies were limited due to small sample sizes, insufficient randomization, and non-blinded assessment. The phenomenon of pre-emptive analgesia was also widely studied among other types of surgery (Nikolajsen et al. 1997).

In a RCT of 60 patients, patients scheduled for amputation were stratified according to the intensity of preoperative pain and then randomized to preoperative epidural analgesia or conventional analgesia. In this study, there was a significant difference in pain experienced before surgery between the epidural and control group. However, the preoperative epidural did not affect the rate of phantom limb pain during the 12-month follow-up period (Nikolajsen et al. 1997).

In addition to preoperative pain and the preoperative analgesics used, factors that may contribute to postoperative pain after amputation are younger age, anxiety, psychological distress, depression, sleeping difficulties and a high expectation of postoperative pain, which is associated with postoperative pain in previous studies on surgical patients (Ip et al. 2009, Sobol-Kwapinska et al. 2016).

2.2.3 TREATMENT MODALITIES OF ACUTE POSTOPERATIVE PAIN AFTER AMPUTATION

Studies on acute pain after amputation are limited as the majority of studies on amputations are focused on chronic phantom limb pain. The treatment of acute pain after amputation is difficult because the selection of suitable analgesics is very limited due to renal insufficiency and long-acting anticoagulants used for vascular disease and the adverse effects of analgesics that increase with age. Various degrees of dementia and postoperative delirium are also common, which make the assessment of pain and analgesics challenging.

The limited number of studies on acute pain after amputation are focused either on epidural analgesia, CPI, or systemic analgesics.

There is a very limited number of studies that have investigated the efficacy and safety of epidural analgesia after amputations. An RCT of 65 patients going through AKA or BKA evaluated a setting of five different interventions that were different combinations of epidural and conventional analgesia or conventional analgesia only. The study revealed that postoperative pain was significantly lower in all intervention groups that received epidural analgesia compared to conventional analgesia at 48 hours after the operation (Karanikolas et al. 2011). In a RCT of 30 patients going through AKA or BKA, acute pain during the first 3 postoperative days was

significantly lower in the patients that received epidural analgesia than in patients that received continuous perineural sciatic or tibial common peroneal infusion with bupivacaine. In this study, the postoperative amount of opioid analgesic did not differ between groups (Lambert et al. 2001). A RCT on 60 patients going through AKA or BKA revealed a significant decrease in phantom pain at 7 days in a group of patients treated with epidural bupivacaine than patients treated with a sham epidural of saline and conventional analgesics. In this study, the postoperative amount of opioid analgesic did not differ between groups (Nikolajsen et al. 1997).
However, these studies are limited in that they investigated a mixed population of both AKAs and BKAs. Based on anatomical reasons, epidural analgesia may not be as effective in the lower extremities in BKAs as in AKAs. This has not been discussed in the studies and it may lead to bias in the results.
On the basis of four studies that investigated epidural analgesia on acute pain after lower limb amputations, there were no significant differences found in motor block, nausea, vomiting, sedation, confusion, or hallucinations when epidural analgesia was compared to systemic opioid analgesia (Jahangiri et al. 1994, Karanikolas et al. 2011, Wilson et al. 2008, Nikolajsen et al. 1997). There were two cases of transient urinary retention and fecal incontinence reported in a study of 24 patients, all in the epidural group (Jahangiri et al. 1994). In a study of 60 amputees, one case of meningitis and one subcutaneous abscess was reported (Nikolajsen et al. 1997).
There is a limited number of studies that investigated the efficacy and safety of CPI of a local anesthetic after amputation. In this method, an elastomeric (usually multiorificed) catheter is placed into a nerve sheath of the sciatic nerve or tibial or common peroneal nerve during the amputation, and local anesthetic is infused to the nerve sheath to provide analgesia on the residual limb. There is only one prior RCT on this technique, which recruited 21 patients going through AKA or BKA and receiving either a CPI of local anesthetic or a similar infusion of saline for 72 hours. In this study, acute postoperative pain was not reported but the postoperative consumption of opioids was significantly lower in the intervention group (Pinzur et al. 1996). The sample size of this study was very low, and the patients going through AKAs and BKA were included in the same study even though the innervation anatomy is different in the thigh and leg regions. The sciatic nerve divides into two branches (the tibial nerve and the common peroneal nerve) in the popliteal region and therefore placing a catheter into one of these branches is insufficient. In a study of 42 patients going through an AKA, a CPI of ropivacaine for 72 hours diminished acute postoperative pain and opioid consumption during first 5 days compared with conventional analgesia. However, this trial was not blinded as the patients were divided into groups based on the side operated (Uhl et al. 2015).
Wound infections associated with perineural catheters were not observed in six observational studies and one RCT. Pruritus, drowsiness, delirium, sedation, nausea,

vomiting, deep venous thrombosis, pulmonary embolism, chest infection, or death did not increase with perineural catheters (Ayling et al. 2014, Elizaga et al. 1994, Fisher et al. 1991, Grant et al. 2008, Malawer et al. 1991, Pinzur et al. 1996, Uhl et al. 2015). Three studies reported catheter failure in 8% to 24% of patients; failure was due to blocking, disconnection, or incomplete insertion of the catheter. Disconnection was the most common problem that occurred in the postoperative period (Grant et al. 2008, Malawer et al. 1991, Ayling et al. 2014).

Studies on the efficacy and adverse effects of systemic analgesics for acute postamputation pain are limited. A RCT of 41 patients going through AKA or BKA revealed that gabapentin at a dose of 2400 mg/day did not reduce the incidence or intensity of postoperative pain compared with placebo. Gabapentin was administered in addition to epidural analgesia and the pain levels of the patients were relatively low in this study, which affected the sensitivity of the study (Nikolajsen et al. 2006).

In a RCT of 45 patients, perioperatively administered ketamine 0.5 mg/kg intravenous (i.v.) combined with postoperatively administered ketamine i.v. infusion (0.5 mg/kg/h for 72 hours) did not diminish pain compared with placebo after AKA or BKA (Hayes et al. 2004).

In a RCT of 19 patients with acute traumatic amputation of the upper limb, the NMDA antagonist memantine was administered in addition to a continuous brachial nerve plexus block. Memantine reduced the amount of requested ropivacaine bolus injections compared with placebo. The sample size of the study was very small and the amputations were heterogenous, including finger amputations and amputations of the wrist or upper arm region, thus making firm conclusions impossible. When the dose of memantine was increased in this study, nausea, dizziness, headache, and agitation were observed (Schley et al. 2012).

Despite the fact that amputations are still a common procedure, there are no guidelines for postoperative pain management. This may be due to the limited number of studies on acute pain management after amputation.

A case report by Karm et al. described a patient with critical ischemia of the lower leg and multiple comorbidities (severe left ventricular dysfunction, pulmonary hypertension, high risk of thromboembolism requiring anticoagulants) who was scheduled for an AKA. The anesthesia risks were evident and the procedure was performed under a combination of multiple ultrasound-guided nerve blocks with 60 ml of local anesthetic mix consisting of 30 ml lidocaine (10 mg/ml) and 30 ml of ropivacaine (3.75 mg/ml). The nerve blocks administered were a sciatic nerve block (25 ml) via a transgluteal approach, a femoral nerve block (20 ml) under the inguinal fossa, and a lateral femoral cutaneous nerve block (7 ml) at the origin of the sartorius muscle and the anterior branch of the obturator nerve (8 ml) between the adductor brevis and longus muscles. The amputation was performed under this combination of nerve blocks (Karm et al. 2018). This approach is interesting and could guide

future studies on continuous nerve blocks for pain after amputation, especially if the sciatic nerve and femoral nerve could both be reached with a CPI after a thigh amputation.

2.2.4 ROPIVACAINE AS A LOCAL ANESTHETIC IN POSTOPERATIVE PAIN AFTER AMPUTATION

Ropivacaine is a long-acting local amide anesthetic structurally related to bupivacaine. Ropivacaine causes reversible inhibition of sodium-ion influx and blocks impulse conduction in nerve fibers. It is a pure S-enantiomer and has a greater degree of motor sensory differentiation, thus causing less motor blockade. Ropivacaine is less lipophilic than bupivacaine and is therefore associated with decreased potential for central nervous system toxicity and cardiotoxicity (McClure et al. 1996). Based on these properties ropivacaine is effective and safe in postoperative pain management after amputations.

2.2.5 TRANSITION FROM ACUTE TO CHRONIC PAIN AFTER AMPUTATION

Stump pain persists and may increase over time in approximately 5% to 10% of patients. Chronic pain is defined as pain that persists or recurs for a period greater than three months (Schug et al. 2019). Chronic stump pain is often associated with sensory abnormalities such as numbness, hyperalgesia, and allodynia (Nikolajsen et al. 2012). The intensity and frequency of phantom pain tends to diminish but may persist and worsen over time (Hsu et al. 2013). Prospective studies indicate that during the first year after amputation 60% to 70% of patients experience phantom limb pain that diminishes in intensity over time. Approximately 60% of patients still have phantom limb pain 7 years after amputation (Halbert et al. 2002). In a cross-sectional study of 914 patients with an earlier amputation during the years 1998 to 2000, 95% of patients reported experiencing pain in the previous 4 weeks. Approximately 80% of these patients experienced phantom pain and 68% experienced residual limb pain (Ephraim et al. 2005).
Persistent pain after amputation is very difficult to treat; no effective treatment has been found even after study of many different analgesic methods (Alviar et al. 2016).

2.2.6 EARLY POSTOPERATIVE MORTALITY AFTER AMPUTATION

A systematic review on 21 studies of lower-limb amputations revealed that early postoperative mortality after AKA and BKA ranges from 4% to 22%. A greater

proportion of early postoperative mortality was observed in those with AKA and older age (van Netten et al. 2016).

2.3 ACUTE PAIN AFTER DAY CASE CHOLECYSTECTOMY

2.3.1 EPIDEMIOLOGY

Approximately 10% to 15% of the adult population has gallstones. Each year, 1% to 4% of those with gallstones experience symptoms, specifically upper abdominal pain that is concentrated on the right side and radiates to the back and scapular zone. These symptoms often become worse after a high-fat meal. Over half a million cholecystectomies are performed annually in the United States (Gurusamy et al. 2014) and 60 000 are performed annually in the United Kingdom (Jones et al. 2012). In Finland, 7992 laparoscopic cholecystectomies were performed in 2018 (National Institute for Health and Welfare); approximately 70% to 80% of these procedures were performed as day-case surgery. Similar pain symptoms as those of gallstones can also manifest in patients without gallstones. A review of 38 studies that investigated postcholecystectomy symptoms revealed that up to 33% of patients operated for gallstones experience similar symptoms postoperatively (Lamberts et al. 2013).

Postoperative pain together with postoperative nausea is the most common reason for delayed discharge after day-case laparoscopic cholecystectomy; approximately 17% to 41% of unplanned overnight stays are due to postoperative pain (Vaughan et al. 2013, Bisgaard et al. 2006).

A study of 230 745 patients going through day-case laparoscopic cholecystectomy in the United States between 2009 to 2011 revealed pain as the reason for in hospital readmission in 12% of the cases (Rosero et al. 2017). Even though postoperative pain after laparoscopic cholecystectomy is manageable with conventional analgesics in most cases, a minority of patients suffer from severe acute pain after laparoscopic cholecystectomy (Vaughan et al. 2013).

2.3.2 TREATMENT OF ACUTE POSTOPERATIVE PAIN AFTER LAPAROSCOPIC CHOLECYSTECTOMY

According to a recent update on the PROSPECT (Procedure-specific postoperative pain management) recommendation implied by Barazanchi et al., based on a review of 258 studies concerning postoperative pain management after laparoscopic cholecystectomy, a multimodal analgesic technique with paracetamol, NSAIDs or cyclooxygenase-2 specific inhibitors, dexamethasone, and troachar wound local anesthetic infiltration is recommended for analgesia after laparoscopic

cholecystectomy. Opioids are recommended only for rescue analgesia postoperatively, as most patients do not require opioids after laparoscopic cholecystectomy. Low-pressure pneumoperitoneum, saline lavage after surgery, and aspiration of the pneumoperitoneum postoperatively is recommended. This evidence-based guideline does not recommend routine use of gabapentinoids, intraperitoneal local anesthetics, or transversus abdominis plane blocks (Barazanchi et al. 2018). It is worth noting that in the studies included in this review and guideline, adjuvant analgesics such as gabapentinoids and nerve blocks were studied in a procedure-specific manner. This approach excludes the individual differences between patient pain levels after the same procedure, patient demographics, or individual risk factors that have an effect on postoperative pain.

A Cochrane Database systematic review of 25 studies and 2505 patients for pharmacological interventions for prevention and treatment of postoperative pain after laparoscopic cholecystectomy revealed that the evidence for analgesics as such as paracetamol, NSAIDs, opioids, and anticonvulsant analgesics is of very low quality. Further trials of low bias risk were recommended. The review also stated that the trials should have other outcomes besides pain, such as quality of life and time to return to work (Gurusamy et al. 2014).

A Cochrane Database systematic review of 19 studies and 1263 patients revealed that although the evidence of local anesthetic infiltration in pain reduction after laparoscopic cholecystectomy is of very low quality, serious adverse events related to the technique are rare (Loizides et al. 2014).

Transversus abdominis plane block (TAP) is a technique that anesthetizes the abdominal wall. A Cochrane Database systematic review revealed that there is only limited evidence supporting the use of perioperative TAP block in reducing opioid consumption, pain scores, or postoperative nausea or sedation after laparoscopic abdominal surgery (Charlton et al. 2010).

TAP as postoperative analgesic after laparoscopic cholecystectomy has been studied after the Cochrane review in a RCT of 80 patients going through elective day-case laparoscopic cholecystectomy. Although acute postoperative pain in coughing was significantly lower in the TAP group, there were no differences in PAR when compared to placebo. Opioid consumption was significantly lower in the TAP group. There were no differences in side effects between groups (Petersen et al. 2012).

Rectus sheet block (RSB) has been studied in a randomized controlled trial of 75 patients going through laparoscopic cholecystectomy. Postoperative pain levels and the consumption of rescue analgesics was lower in the RSB group compared to intraperitoneal local anesthetic infiltration or conventional analgesia (Gupta et al. 2016). In a RCT of 200 patients going through laparoscopic cholecystectomy, the infiltration of RSB preoperatively was compared to the infiltration of the nerve block

postoperatively. The preoperative infiltration resulted in significantly lower postoperative pain levels (Jeong et al. 2019).
As TAP and RSB are relatively easy and safe to perform in a ultrasound-guided technique without any side effects, these techniques could be added to pain management in situations of severe postoperative pain. These techniques may also be considered if several risk factors for postoperative pain are present. Although single-shot nerve block may offer effective analgesia in the immediate postoperative period, the effect is of brief duration (approximately 16-24 hours). The patient should be adequately informed of this limitation and provided with relevant pain medication when discharged.

2.3.3 GABAPENTINOIDS AS ADJUVANTS IN POSTOPERATIVE PAIN MANAGEMENT AFTER LAPAROSCOPIC CHOLECYSTECTOMY

Gabapentinoids, pregabalin, and gabapentin are used in the treatment of acute postsurgical pain to decrease opioid consumption and adverse effects and to improve postoperative analgesia (Tiippana et al. 2007, Kumar et al. 2017). The use of gabapentinoids in the treatment of postoperative pain is off-label. Studies on gabapentinoids in day-case cholecystectomy show conflicting results. While gabapentinoids appear to decrease pain intensity, they may also cause more adverse effects (such as dizziness and fatigue) compared to placebo and may consequently delay hospital discharge (Agarwal et al. 2008, Balaban et al. 2012, Zhang et al. 2011, Li et al. 2017). Recent systematic reviews on mixed surgical populations conclude that the effect of perioperative gabapentinoids is less impressive than previously reported (Fabritius et al. 2016, Fabritius et al. 2017).
A limitation of these studies on gabapentinoids for postoperative pain was that the studies were based on type of operation instead of the individual demographic and psychological risk factors that contribute to postoperative pain. Adjuvant medications such as gabapentinoids may be beneficial in patients with several risk factors for postoperative pain.
Pregabalin is a γ-aminobutyric acid analogue that binds to voltage-gated calcium channels. It reduces the hyperexcitability of the dorsal horn neurons induced by tissue damage. As surgical stimuli leads to sensitization of dorsal horn neurons, pregabalin might affect postoperative pain (Mishriky et al. 2015).

2.3.4 TRANSITION FROM ACUTE TO CHRONIC PAIN AFTER LAPAROSCOPIC CHOLECYSTECTOMY

Acute pain after laparoscopic cholecystectomy tends to diminish over time but may become persistent and increase in intensity. It is estimated that 3% to 56% of patients

experience persistent pain (defined as pain lasting ≥3 months) after laparoscopic cholecystectomy (Macrae et al. 2001, Perkins et al. 2017, Berger et al. 2003). In a review of 38 studies on laparoscopic cholecystectomy, 33% of patients experienced persistent pain after surgery and 14% experienced persistent postoperative pain as a new symptom (these patients were primarily painless before operation) (Lamberts et al. 2013). In a follow-up study of 150 patients going through laparoscopic cholecystectomy, 13% of patients experienced moderate-to-severe pain 1 year after surgery. The risk of persistent pain was significantly associated with the intensity of acute postoperative pain (Bisgaard et al. 2005). In a follow-up study of 100 patients going through laparoscopic cholecystectomy, 9% experienced persistent pain at 1 year after surgery, and the incidence of persistent pain was associated with acute postoperative deep abdominal pain during the first postoperative week (Blichfeldt-Eckhardt et al. 2014).

2.4 RISK FACTORS FOR ACUTE POSTOPERATIVE PAIN

Risk factors for postoperative pain have been a studied, as the intensity of postoperative pain depends not only on the procedure performed but also on differences between patients.

The individual risk factors have been widely studied. The studies seem to be heterogenous, with many different study designs and study questions. The results of different studies were evaluated and analyzed in three thorough systematic reviews (Ip et al. 2009, Sobol-Kwapinska et al. 2016, Yang et al. 2019). As these reviews indicate, the results of individual studies on risk factors are somewhat controversial and at this point it is challenging to say which risk factors are more important and more reliable predictors than others and what are the underlying mechanisms for these factors to act as predictors of postoperative pain.

A review of 48 studies and 23 037 patients undergoing various surgical procedures revealed that preoperative anxiety, preexisting pain, younger age, and type of surgery were the strongest predictors of postoperative pain. Gender was not observed to correlate with postoperative pain in this review (Ip et al. 2009).

A review by Sobol-Kwapinska et al. of 53 studies and 10 749 patients on the psychological risk factors for postoperative pain revealed that pain catastrophizing, optimism, the expectation of pain, neuroticism, anxiety (state and trait), negative affect, and depression were predictors for postoperative pain (Sobol-Kwapinska et al. 2016). Twenty-seven of these studies were not included in the review of Ip et al.

A recent systematic review and meta-analysis of 33 studies and 53 362 patients was conducted. To be included in this review, a measure of association between poor postoperative pain control (defined by the study authors) and at least one preoperative predictor for postoperative pain were required. Significant preoperative

predictors of postoperative pain based on this review included younger age (14 studies), female gender (20 studies), smoking (9 studies), a reported history of depressive symptoms (8 studies), reported history of anxiety symptoms (10 studies), sleep difficulties (2 studies), higher body mass index (BMI) (2 studies), presence of preoperative pain (13 studies), and use of any kind of preoperative analgesia (not only opioids; 6 studies). The factors that were not associated with poor postoperative pain control in this review were pain catastrophizing, chronic pain, American Society of Anesthesiologists (ASA) status, marital status, socioeconomic status, education, surgical history, preoperative pressure pain tolerance, and orthopedic surgery versus abdominal surgery. Chronic pain was investigated in three studies; an association with postoperative pain was observed in one study but not in the other two (Liu et al. 2012, Sanansilp et al. 2016, Caumo et al. 2012). Pain catastrophizing was assessed in three studies; an association with postoperative pain was observed in two trials (Rakel et al. 2012, Lunn et al. 2013, Baudic et al. 2016). Although this review emphasized the role of some predictive factors, the review had some limitations. Day-case surgical operations were excluded from this review. The outcomes of the studies differed and three different outcome measures were used (NRS, VAS, and VRS). In some studies, significant pain was rated as pain >4 on NRS but was >5 in other studies; NRS was not reported in some studies. Postoperative pain as an outcome was mainly measured at 24 to 48 hours after surgery although there were exceptions. Although the predictors assessed included a history of depressive symptoms, how these symptoms were assessed was not described. This was also the case with the predictive factor of history of anxiety symptoms. Some important studies on risk factors were also missing from this review, such as the article by Sipilä et al. that examined the predictive role of anxiety and the expectation of pain in over 500 breast cancer patients (Sipilä et al. 2017). Due to these limitations, the meta-analysis conducted may not be completely free of bias (Yang et al. 2019).
In an observational study on 22 963 German patients from 2004 to 2010 that underwent 30 different surgical procedures, younger age, chronic pain, preoperative pain, and female gender in addition to the type of surgery were associated with postoperative pain (Gerbershagen et al. 2014). This study did not discuss the role of different surgical techniques of individual surgeons on postoperative pain.

2.4.1 DEMOGRAPHIC RISK FACTORS FOR POSTOPERATIVE PAIN

Demographic risk factors for postoperative pain differ from other risk factors as they are easily detectible and their assessment does not require extensive evaluation. This may be one reason why they have been widely studied. According to many studies, some demographic risk factors (such as younger age) seem to predict postoperative

pain. However, for other demographic risk factors the evidence is somewhat controversial.
A review of 48 studies and 23 037 patients on the risk factors of postoperative pain revealed that younger age was associated with postoperative pain in six studies. Gender, BMI, weight, ASA classification, or education level were correlated with postoperative pain only in isolated studies and were not observed to be predictive factors of postoperative pain (Ip et al. 2009). In a recent review of 32 studies on the risk factors of postoperative pain published after Ip et al., younger age, female gender, smoking, sleep difficulties, presence of preoperative pain, and use of analgesics were associated with postoperative pain. In contrast, chronic pain, ASA classification, marital status, socioeconomic status, education, surgical history, and preoperative pressure pain threshold were not observed to be associated with postoperative pain (Yang et al. 2019).

2.4.2 ANXIETY

Anxiety has been the most common psychological predictive factor in several studies. In most studies, anxiety was assessed with The Spielberger State-Trait Anxiety Inventory (STAI), the Hospital Anxiety and Depression Scale, or a self-evaluated VAS score from 0 to 100. Based on the reviews that assessed the studies of preoperative risk factors for postoperative pain (Ip et al. on 2009, Sobol-Kwapinska et al. 2016, and Yang et al. 2019), there are a total of 34 studies that support the observation that preoperative anxiety predicts postoperative pain. Seven of the studies were in gastrointestinal surgery (Boeke at al. 1991, De Cosmo et al. 2008, Taenzer et al. 1986, Caumo et al. 2002, Granot et al. 2005, Scott et al. 1983, Belii et al. 2014), eight in obstetrics or gynecology (Pan et al. 2006, Rudin et al. 2008, Munafo et al. 2003, Hsu et al. 2005, Kain et al. 2000, Pud et al. 2005, Borges et al. 2016, Gorkem et al. 2016), five in a mixed surgical population (Sommer et al. 2010, Aubrun et al. 2008, Gramke et al. 2009, Kalkman et al. 2003, Mamie et al. 2004), of which one studied day-case surgery (Gramke et al. 2009), three in orthopedics (Pinto et al. 2014, Petrovic et al. 2014, Robleda et al. 2014), four in breast surgery (Kaunisto et al. 2013, Ozalp et al. 2003, Rehberg et al. 2017, Katz et al. 2005), three in thoracic surgery (Weissman-Fogel et al. 2009, Grosen et al. 2014, Bachiocco et al. 1990), one on thyreoidectomies (Kil et al. 2012), and one on ear, nose and throat surgery (Sommer et al. 2009).
In addition to these studies, a study on 563 patients undergoing breast surgery due to breast cancer revealed that preoperative anxiety is associated with postoperative pain. In this study, patient psychological distress was evaluated by a sum score of the Beck Depression Inventory and the State Trait Inventory. This sum score correlated with acute postoperative pain. The patients were asked to evaluate the

preoperative expectation of postoperative pain on a scale of 0 to 10 and higher expectations were associated with postoperative pain. Pain resolution was slower in patients with high psychological distress and a high expectation of pain (Sipilä et al. 2017).

In an observational study of 200 women undergoing cesarean section, the risk for postoperative pain was evaluated with three questions. Anxiety was assessed by a VAS with the question "On a scale of 0-100, how anxious are you about your upcoming surgery?". The expectation of postoperative pain was assessed by a VAS with the question: "On a scale of 0-100, with 0 being no pain and 100 being the worst imaginable pain, how much pain do you anticipate to experience after your upcoming surgery?". The expected amount of postoperative analgesic required was assessed with a five-item questionnaire, with 1 being much less than average and 5 being much more than average. In this study, the association of the experience of loudness of three series of audio tones with postoperative pain was evaluated. These three questions (VAS anxiety, VAS expectation of pain, and the expectation of the amount of postoperative analgesics needed) all correlated with MEP at 24 hours after surgery. The association was not observed at 18 hours after surgery. The audio tone evaluation did not correlate with postoperative pain (Pan et al. 2013). The risk factor evaluation for anxiety, expectation of pain, and the expectation of analgesic amount needed was performed in a simple manner in this study, with three questions, two assessed with VAS and one on a five-item questionnaire. This indicates that a questionnaire could be used as part of a routine preoperative evaluation. Time-consuming questionnaires (such as STAI) in the evaluation of anxiety are not useful in the preoperative evaluation of patients in clinical situations where time is limited. This seems to be the case in many studies on psychological risk factors of postoperative pain, as the questionnaires are not suitable for clinical use due to their length and complexity.

2.4.3 EXPECTATION OF PAIN

The expectation of pain was associated with acute postoperative pain in seven studies from a review of 53 studies (Bisgaard et al. 2001, Desai et al. 2012, Gramke et al. 2009, Mamie et al. 2004, Montgomery et al. 2010, Pan et al. 2006, Sommer et al. 2010). Pain expectation was associated with acute postoperative pain and slower resolution of postoperative pain in breast cancer patients undergoing surgery (Sipilä et al. 2017). There are studies that report contradictory results on pain expectation as a risk factor. This may be due to the fact that heterogenous definitions for the expectations of pain are used in different studies. For example, a pain expectation score >40 may be evaluated as significant on a VAS scale or pain expectation can be evaluated as a dichotomous variable (low or high expectation of pain).

2.4.4 SLEEP QUALITY

A study of 108 patients undergoing breast cancer surgery were assessed for sleeping difficulties via preoperative questionnaire. Patients with poor sleep quality reported higher postoperative pain scores during 24 hours after surgery, required more analgesics, experienced more complications, and had a longer hospital stay (Wang et al. 2019). A study of 454 patients undergoing various surgical procedures were assessed for chronic sleeping difficulties via questionnaire. Sleeping difficulties were associated with postoperative pain (Mamie et al. 2014). Another study of 245 women undergoing cesarean section assessed sleep quality with the Pittsburgh Sleep Quality Index questionnaire. In this study, poor sleep quality was associated with postoperative pain (Orbach-Zinger et al. 2016).

2.4.5 DEPRESSION

Depression has been associated with postoperative pain in some studies. A study of 198 women undergoing breast surgery due to cancer revealed an association between the Beck Depression Inventory score and postoperative pain (Rehberg et al. 2017). In an observational study of 346 patients undergoing abdominal surgery, depression as evaluated by the Montgomery-Åsberg Depression Rating Scale (MADRS) was associated with postoperative pain among other predictive factors, such as chronic pain and anxiety via STAI evaluation (Caumo et al. 2002). Depression had a predictive value as a part of the evaluation of psychological distress, as assessed with the Beck Depression Inventory (Sipilä et al. 2017). There are several other studies that investigated psychological distress other than anxiety as predictive factors. These included nonspecific parameters such as patient mood, affect, or personality traits, hostility, or neuroticism. Some of these studies revealed a correlation with these factors and postoperative acute pain (De Cosmo et al. 2008, Mamie et al. 2004, Taenzer et al. 1986, Bisgaard et al. 2001, Caumo et al. 2002, Bachiocco et al. 19990, Ozalp et al. 2003).

2.4.6 CATASTROPHIZING

Pain catastrophizing is a psychologic coping method defined as an exaggerated negative mental set brought to bear during actual or anticipated painful experience. Pain catastrophizing consists of three dimensions, namely rumination, magnification, and helplessness (Sullivan et al. 2001). It is evaluated on a 13-item questionnaire, the Pain Catastrophizing Scale (PCS) (Sullivan et al. 1995).
A review of 53 observational studies on psychological predictors of postoperative pain (Sobol-Kwapinska et al. 2016) revealed that catastrophizing is associated with acute postoperative pain in 21 studies (Gramke et al. 2009, Granot et al. 2005, Grosen

et al. 2014, Hirakawa et al. 2014, Khan et al. 2012, Lunn et al. 2013, Papaioannou et al. 2009, Pavlin et al. 2005, Pinto et al. 2012, Pinto et al. 2013, Pinto et al. 2014, Pinto et al. 2015, Rakel et al .,2012, Roth et al. 2007, Sommer et al. 2010, Strulov et al. 2007, Sullivan et al. 2009, Tolver et al. 2011, Vranceanu et al. 2010, Weissman-Fogel et al. 2009).
The role of catastrophizing in the prediction of postoperative pain is somewhat controversial. In some studies, catastrophizing seems to be associated with postoperative pain, and in some studies it is not. Catastrophizing might be relevant in some cases as part of the risk evaluation for postoperative pain, but the catastrophizing scale alone does not solely seem to be a reliable predictive tool. On the other hand, the catastrophizing scale consists of 13 questions and might be time consuming as a part of a wider evaluation of the risk of postoperative pain.

2.4.7 PROCEDURE-SPECIFIC RISK FACTORS

In a German register study of 50 523 patients in 105 German hospitals, 179 surgical procedures were compared according to acute postoperative pain on the first postoperative day. Forty operations with the highest pain scores included 22 orthopedic or trauma operations on the extremities. The 25 operations with the highest pain scores included appendicectomies, cholecystectomies, and tonsillectomies. A number of major abdominal surgeries traditionally associated with severe postoperative pain were not on this list, probably due to use of epidural analgesia (Gerbershagen et al. 2014). Another study of 1123 patients that investigated day-case surgery revealed that the procedures with the highest postoperative pain scores were shoulder, dental, anal, tendon, bursae, and fasciae surgery. Some procedures that are routinely performed in a day-case manner in other centers were excluded, such as anterior cruciate ligament surgery of the knee (Vrancken et al. 2018). In a study of 648 day-case surgery patients, operations of the ear, nose, and throat, abdominal operations, and plastic surgery of the breasts were the most painful operations during first 48 postoperative hours (Gramke et al. 2007).

2.5 CLINICAL PREDICTION TOOLS OF POSTOPERATIVE PAIN

Despite the large number of studies on different predictive factors, there are few validated tools that can be used preoperatively by the anesthesiologist to evaluate patients risk of pain. Such tools are rare and are not commonly used. In addition they are time-consuming and therefore do not suite well for clinical practice.
A nomogram for the evaluation of acute postoperative pain was developed in 2003 and a validation was performed in 2009 (Kalkman et al. 2003, Janssen et al. 2009).

The nomogram assesses preoperative factors such as gender, age, preoperative pain score, type of surgery (ophthalmology, laparoscopy, orthopedic, abdominal, or other), preoperative anxiety, need for information on the six-item Amsterdam Preoperative Anxiety and Information Scale (APAIS) (Moerman et al. 1996), and incision size. This nomogram has been used by the authors in both day-case and inpatient hospital surgery. However, the authors report that the estimates of the sensitivity and specificity of the scoring appear low, which probably is the case in most of the risk evaluation tools to date.

A simple tool has been developed for the prediction of persistent postoperative pain risk in breast cancer surgery for clinical use. This tool is based on evidence of studies in this specific patient group. Factors considered include BMI (<31 or ≥31 kg/m2), average pain at the site operated during the week before the operation on NRS, if axillary dissection is performed, and evaluation of postoperative pain on first postoperative and seventh postoperative days (Meretoja et al. 2017). This tool is designed for screening patients at risk for persistent pain, to enhance pain management, and to prevent chronification of pain. A similar tool for the evaluation of acute postoperative pain would be very useful.

The brief measure of emotional preoperative stress (B-MEPS) index was developed to detect the risk of postoperative pain in surgical patients. The index consists of 15 questions on distress, anxiety, and psychological factors that contribute to the risk of postoperative pain. The questions were constructed by modifying the reduced version of the State-Trait Anxiety Inventory (STAI-S-T), the MADRS, the WHO Self-reporting Questionnaire (SRQ-20), and the Future Self-perception Questionnaire (FSPQ) (Caumo et al. 2016).

A study of 571 day-case surgery patients undergoing various surgical procedures revealed that the factors that predict postoperative pain were younger age, the anticipated pain level from the clinician's point of view, female gender, education level, preoperative pain, the expectation of pain, short-term and long-term fear for the upcoming operation, low optimism (<28) on the Life Orientation Test (LOT; eight items that measure personality trait optimism), and high pain catastrophizing (>11) on the PCS (Gramke et al. 2009). These factors were used to create a predictive model for clinical use and was planned to be validated on a different patient group (Altman et al. 2009). The validation was performed on a mixed day-case surgery population of 1118 patients; however, the combination of these factors did not predict acute postoperative pain (Stessel et al. 2017).

It has been suggested that a tool to assess preoperative emotional stress would enable the addition of more specific interventions to procedure-specific pain treatment for patients who are at a greater risk of pain. An accurate measure of the psychological risk factors may facilitate directing preoperative psychological preparation. Such preparation appears to improve postoperative outcomes and can even have an effect

on physiological and immunologic function (Johnston et al. 1993, Segerstrom et al. 2004).

2.6 PREOPERATIVE PSYCHOLOGICAL PREPARATION

Cochrane Database systematic review investigated if psychological preparations such as procedural information, sensory information, cognitive intervention, relaxation, hypnosis, or emotion-focused interventions had an impact on postoperative pain, behavioral recovery, length of hospital stay, and negative affect. The review included 105 studies and 10 302 patients. A total of 61 studies had postoperative pain as an outcome. Twenty-seven studies were on cardiothoracic surgery; this seems to be the surgical specialty where most work has been done to investigate the possibilities of psychological interventions for postoperative pain. Seventeen studies were on coronary bypass surgery, 22 studies investigated hip or knee replacement surgery, seven cholecystectomies, seven hysterectomies, two breast surgery, and 31 were on various surgical procedures. A variety of psychological components were used in interventions and many were frequently combined. There was low-quality evidence to support that psychological preparation techniques are associated with lower postoperative pain, behavioral recovery, negative affect, and length of hospital stay. Such preparation techniques were very unlikely to be harmful. Results were similar for all categories of intervention and no specific psychological intervention seemed to work better than others. The quality of studies was reported to be generally low due to poor reporting and there was heterogeneity in surgery types, interventions, and outcomes. (Powell et al. 2016).

2.7 TARGETING PAIN MANAGEMENT BASED ON PATIENT-SPECIFIC RISK FACTORS

The risk factors for postoperative pain have been studied for over 30 years and there are many studies on this topic. It is thus surprising how few studies sought to improve postoperative pain management based on risk factors. This could be due to the fact that there is no current consensus of risk factors and a validated tool for evaluating postoperative risk factors for pain does not exist.

Targeting consists of directing more effective analgesia for patients at risk of postoperative pain. The goals of targeting include improving postoperative pain outcomes, reducing side effects, and enhancing recovery. Targeting was studied in a randomized controlled trial of 74 women undergoing cesarean section who were first evaluated for the risk of postoperative pain via a short three-item questionnaire (Pan et al. 2013). The questions addressed anxiety, the expectation of pain, and the expectation of analgesic amount needed. The patients randomized to the intervention

were those predicted to be >80th percentile for evoked pain intensity based on this questionnaire. The intervention was a higher or lower dose of intrathecal morphine combined to acetaminophen or placebo. There was a significant difference in acute pain at 24 hours after surgery between groups (Booth et al. 2016). However, it is not clear if this difference would have been observed if the entire whole cohort of patients was included in the study without preoperative risk factor screening; it is possible that the better postoperative pain outcome was achieved by using a higher dose of intrathecal morphine and oral acetaminophen. This emphasizes that studying the targeting of pain management is complex and studies should be designed carefully.

In a RCT on patients undergoing total knee arthroplasty, 1110 patients were assessed for pain catastrophizing via the PCS. Thirty-two percent of patients with the highest scores were randomized to receive 10 mg escitalopram or placebo 7 days after surgery and on the day of surgery. There were no differences between groups regarding acute postoperative pain outcomes or side effects (Lunn et al. 2015). The timing of escitalopram was not optimal in this study as it was started on the day of operation; escitalopram is known to be effective in anxiety disorders at 2 weeks (Baldwin et al. 2009).

2.8 TRANSITION FROM ACUTE TO CHRONIC POSTSURGICAL PAIN

The transition from acute to chronic postsurgical pain is a complex process that involves multiple mechanisms, including persistent peripheral inflammation, peripheral sensitization, central sensitization, psychosocial issues, and genetic factors (Chapman et al. 2017, Deumens et al. 2013.) It seems that descending modulatory systems are an important factor in the development of persistent pain (Yarnitsky et al. 2010). The incidence of chronic postsurgical pain ranges from 5% to 75% depending on the surgical procedure (Deumens et al. 2013, Steyaert et al. 2018). Individual risk factors have a remarkable effect on the development of chronic postsurgical pain. Female gender, younger age, the presence and severity of preoperative pain both at the site operated on and on other sites, preoperative opioid analgesics, and preoperative psychological distress (anxiety, pain catastrophizing, depression, and posttraumatic stress disorder) have been reported to increase the risk for chronic postoperative pain in many studies (Steyaert et al. 2018, Chapman et al. 2017, Hinrichs-Rocher et al. 2009, Theunissen et al. 2012, Katz et al. 2015, Smith et al. 2017, Kleiman et al. 2011). Other studies have indicated an association between the intensity of acute postoperative pain and chronic postsurgical pain. However, it is not clear if aggressive treatment of acute postoperative pain reduces the risk of chronic postoperative pain (Gilron et al. 2017, Fletcher et al. 2015). In a recent

observational study of 593 patients undergoing various surgical procedures, 41% of patients had pain of any kind and 8% had neuropathic pain preoperatively. At the first postoperative day, 72% had pain and 5% reported neuropathic pain. At the second postoperative day, 13% had neuropathic pain. After 2 months, 333 patients were evaluated for postoperative persistent pain, which occurred in 33% of the patients. It was observed that acute neuropathic pain on the day of surgery or the first postoperative day is associated with persistent postoperative pain. Neuropathic pain was evaluated with the clinician-administered Neuropathic Pain Diagnostic Questionnaire (DN4) or the Self-administered Neuropathic Pain Diagnostic Questionnaire (DN2) (Beloeil et al. 2017). These findings emphasize the importance of a follow-up outpatient clinic for the patients with severe acute postsurgical pain, particularly if neuropathic components are present. Several studies have focused on the prevention of chronic postsurgical pain and revealed conflicting results (Steyaert et al. 2018), likely due to multiple factors. The complex transition from acute to chronic pain can be difficult to prevent with a single treatment method. Furthermore, the study interventions often concentrated on the acute postsurgical phase, but the transition from acute to chronic pain is likely a lengthier process. One particularly important factor is that the studies conducted thus far have been based on surgery type and the individual risk factors have not been considered in study design; patients should be stratified by risk factors for postoperative pain and interventions should be targeted based on risk factor profiles. This is also a limitation of studies on acute postoperative pain. Targeted studies are likely in progress now and will be published in the upcoming years.

3 AIMS OF THE STUDY

The purpose of the present work was to examine acute postoperative pain and associated treatment options and risk factors for patients undergoing laparoscopic day-case cholecystectomy or thigh amputation.

The specific aims of this thesis study were:

1. To evaluate the efficacy and safety of various analgesic techniques on acute postoperative pain after major limb amputation (I).

2. To evaluate the efficacy of a CPI of local anesthetic combined to a wound infusion for the treatment of postoperative pain after AKA in patients with peripheral vascular disease (II).

3. To investigate the individual demographic and psychological risk factors for postoperative pain, including the expectation of pain, fear of pain, anxiety, patients´ need for more information about postoperative pain and pain management, and their correlation with acute postoperative pain in range of procedures among elective surgical patients (III).

4. To investigate a short five-item questionnaire in evaluating the risk of postoperative pain in day-case cholecystectomy and to assess the efficacy and safety of a targeted single-dose preoperative pregabalin in a high-risk group of patients (IV).

4 MATERIALS AND METHODS

4.1 ETHICAL CONSIDERATIONS

Studies II, III, and IV were approved by the Institutional Ethics Committee. Studies II and IV were approved by the Finnish Medicines Agency (Fimea). Written informed consent was obtained from all patients in studies II, III, and IV. Studies II and IV were registered prior to patient enrollment in the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

4.2 PATIENTS

Study II included Finnish-speaking patients with critical ischemia due to peripheral vascular disease and a planned AKA, were aged ≥18 years, were able to use the VRS to evaluate pain, and had estimated life expectancy >2 weeks according to the assessment of the treating anesthesiologist. Exclusion criteria before randomization included revision surgery and bilateral amputation, and lack of informed consent.
Study III included elective surgical Finnish-speaking patients aged >17 years scheduled for any kind of elective surgery during 2009 to 2010. Exclusion criteria were inability to answer the questionnaires and planned postoperative intensive care.
Study IV included patients scheduled for an elective, day-case laparoscopic cholecystectomy. Adult patients aged >18 years but <70 years with an ASA classification <3, weight >50 kg, BMI <40 kg/m², who were not pregnant or breast feeding, who did not have allergies or significant adverse effects to the medications used in the protocol, and able to use the NRS scale and to communicate in the Finnish language were included.

4.3 STUDY DESIGNS

Study I is a systematic review. Studies II and IV are RCTs where analgesic methods were assessed in a placebo-controlled setting for postoperative pain after surgery. Study III is a prospective observational study.

4.3.1 SEARCH STRATEGY, SOURCES, ELIGIBILITY, AND OUTCOMES OF THE REVIEW (STUDY I)

The systematic review (Study I) was performed according to the standards described in the PRISMA statement (Moher 2009). A literature search was performed in PubMed (1964-2017), Cochrane Central Register of Controlled Trials (April 2017), and Cochrane Database of Systematic Reviews (2005-2017) using the following key words: ((amputation) AND (pain OR analgesi* OR pain relief)) AND (acute OR postoperative). RCTs and observational studies on analgesics and regional analgesia for acute postoperative pain following major limb amputations for any indication (peripheral vascular disease, malignant disease, trauma) were included. Major limb amputation was defined as amputation above knee or below knee but proximal to the ankle, or upper limb amputations proximal to the wrist. Study period for acute pain was defined as 2 weeks after the operation, based on clinical experience. Data from studies on treatment of chronic pain following amputation were included if results during the immediate postoperative period of 2 weeks were reported; studies reporting on any type of acute postoperative pain, stump pain, or phantom pain were included. All RCTs and observational studies with a minimum of 10 patients with clearly described methods and a control group were included. The primary outcomes of the systematic review were the incidence and intensity of acute stump and phantom pain. Secondary outcomes included the incidence and intensity of preoperative pain, opioid consumption in the first 72 hours, the incidence and intensity of chronic stump and phantom pain, and adverse effects. A total of 940 patients undergoing major amputations were included in the systematic review. Patient data were retrieved from 19 studies on different analgesic methods and their adverse effects in the treatment of acute pain after major amputations. The review covered the literature from 1964 to April 2017.

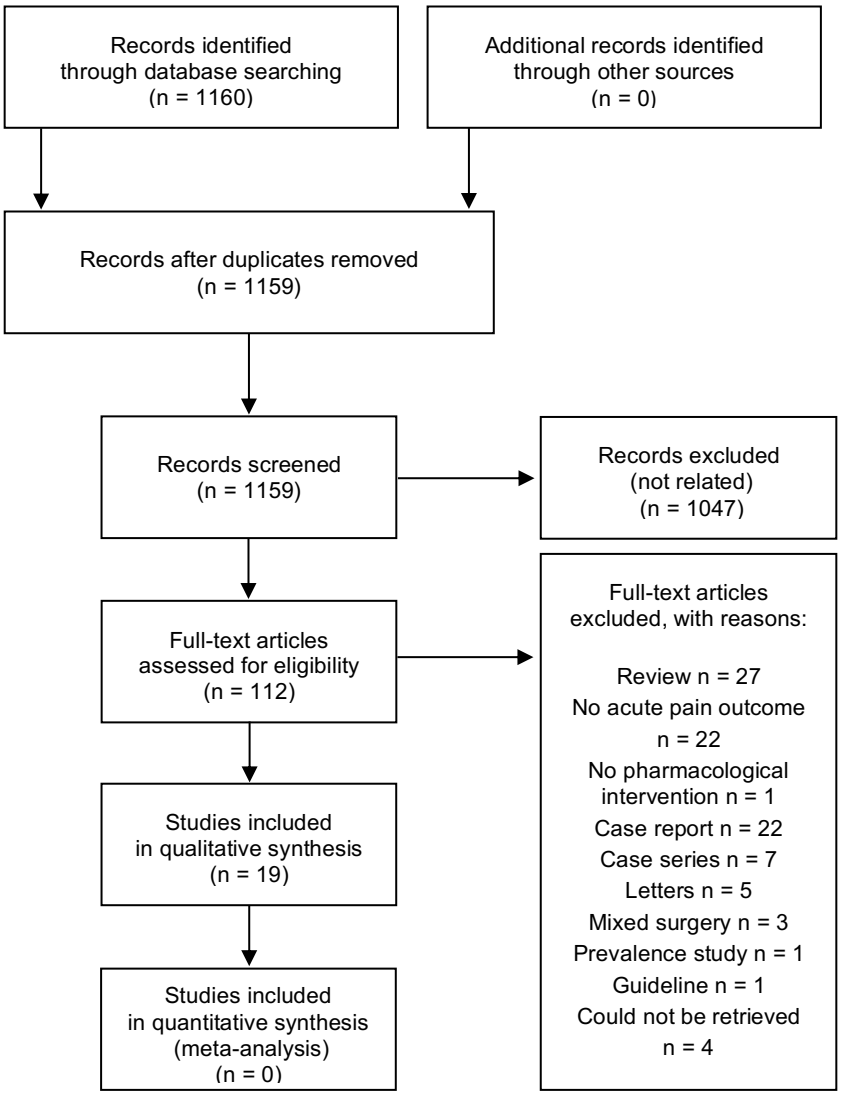

Figure 2. PRISMA flow chart of the systematic review (study I).

4.3.2 STUDY DESIGNS, PROTOCOLS AND INTERVENTIONS (STUDIES II AND IV)

Study II was a randomized, controlled multicenter study of 89 patients undergoing AKA that investigated the safety and efficacy of a combination of CPI and local anesthetic wound infusion compared to placebo. Study II was performed in the surgery departments of six hospitals in Finland during the period from August 2014 to September 2016. The study was conducted according to the standards described

in the CONSORT guidelines (Schulz et al. 2010). Each center had a site principal investigator who arranged study recruitment in the center. Randomization was conducted as two-group 1:1 block randomization using a computer-generated allocation list at Jorvi Hospital. All other study personnel, except for the nurse who prepared the study infusion and did not otherwise participate in patient care, and the study participants were blinded to group allocation.

At the end of the procedure, one elastomeric multiorificed catheter was inserted into the sciatic nerve sheath and one under the fasciae in the wound area. The catheter type was not specified and any product with orifices on 7.5-12 cm was accepted, and any type of infusion device capable of delivering 2 ml/h to two catheters could be used. The nerve sheath catheter was tunneled to avoid detachment. A 10-ml bolus of ropivacaine 0.75% was delivered to both catheters directly after catheter placement and the infusion was initiated immediately to avoid blocking of the catheters. Written instructions and an instructional video of the placement and attachment of the catheters prepared by the investigators were used to guide the surgeons in advance to perform the procedure correctly and to standardize the technique of catheter placement. The perineural infusion of ropivacaine 0.2% in the intervention group and saline in the placebo group was delivered to two catheters at a rate of 2 ml/hour each for 72 hours postoperatively. The dosing of ropivacaine was decided when designing the study, based on the clinical experience of the principal anesthesiologists at the study centers. Either general anesthesia or spinal anesthesia was used for the surgery. As a standard medication, patients received paracetamol 1 g orally three times daily. The analgesics used by the patient prior to the operation were continued postoperatively. Intramuscular (i.m.) or per oral postoperative oxycodone was provided as needed.

In the double-blind, placebo-controlled, multi-arm parallel clinical study investigating targeted preoperative pregabalin in day-case cholecystectomy (study IV), all patients scheduled for an elective, day-case laparoscopic cholecystectomy in the day surgery department of Jorvi Hospital, Helsinki University Hospital, Finland, were assessed for eligibility between March and September 2016. The study was conducted according to the standards described in the CONSORT guidelines (Schulz et al. 2010). Patients were allocated to a study group or a follow-up group based on a preoperative five-item questionnaire assessing the risk of postoperative pain. The questionnaire was administered by a preoperative nurse in a telephone interview. Details on the questionnaire are shown in Table 2.

Table 2. Preoperative questionnaire and scoring for the risk of postoperative pain in study IV.

1.	Have you experienced severe pain after surgery before?	yes/no
2.	Do you have, or have you had before, pain for 6 months or longer?	yes/no
3.	Based on your previous experiences, do you assume that you need more pain medication that is commonly needed after surgery?	yes/no
4.	How strong do you assume the pain after surgery will be on a scale from 0 to 10?	0-10
5.	How anxious have you felt during the past week on a scale of 0-10?	0-10

YES in questions number 1, 2 and 3 → high risk
Score more than 4 in both questions 4 AND 5 → high risk
YES in one of the questions 1–3 combined to score of 4 or more in either question 4 or question 5 → high risk

The questions were designed based on previous studies on predictive factors (Ip et al. 2009, Caumo et al. 2002, Katz et al. 2005, Pinto et al. 2017, Gramke et al. 2009, Sipilä et al. 2017, Pan et al. 2013). The rating was based on a pilot with 40 ambulatory cholecystectomy patients. The correlations between the risk assessment questions and postoperative pain were evaluated. Patients with several risk factors were allocated to the high-risk group until a total of 60 patients was reached. Patients with fewer risk factors formed the low-risk follow-up group. Altogether 130 patients were recruited. The high-risk group was randomized to receive pregabalin 150 mg (n=30) or placebo (n=30) 1 hour before surgery. The pregabalin dose was decided based on clinical experience. Two group 1:1 block randomization was conducted using block sizes of six. Group allocations and the study medication were concealed in sequentially numbered opaque envelopes. Study medication was prepared in the Central Pharmacy of Helsinki University Hospital. Pregabalin and placebo capsules appeared identical. Study personnel, including the anesthesiologist, surgeon, and nurses performing follow-up outcome assessments, and study participants were blinded to group allocation concerning the placebo and pregabalin groups. The patients were blinded to group allocation concerning all groups. The low-risk follow-up group of 70 patients received standardized and otherwise similar treatment as the study group but without the intervention.
Anesthesia and postoperative analgesics during hospital stay were standardized according to PROSPECT guidelines (Kehlet et al. 2007).

4.3.3 PROSPECTIVE OBSERVATIONAL MULTICENTER STUDY (STUDY III)

The observational study on elective surgical patients (study III) was performed as a prospective observational multicenter study during 2009 to 2010 in six Finnish hospitals (5 in the Helsinki University Hospital district and 1 at Kuopio University Hospital). The study was performed according to the standards of the applicable STROBE guidelines (von Elm et al. 2014).

The information was collected on two questionnaires, one before surgery after meeting the anesthesiologist at the surgical ward or at preoperative outpatient clinic, and the second after surgery during the first 2 postoperative days at the surgical ward. The day-case surgery patients answered the second questionnaire at home before returning it.

Postoperative MEP and PAR were recorded once a day on the day of operation and for 2 postoperative days on NRS. The worst MEP and PAR were recorded. Pain levels were classified as severe (NRS 6-10), moderate (NRS 4-5), and mild (NRS 1-3). Side effects of the analgesics were followed for 2 postoperative days. The overall satisfaction with pain management, hospitalization time, and possible surgical complications during hospitalization were recorded.

4.4 OUTCOME MEASURES

4.4.1 PAIN ASSESSMENT METHODS

Pain was assessed using VRS in study II. The VRS is a five-point scale suitable for patients with dementia or cognitive dysfunction but are able to self-report pain in a simple descriptive scale (Pesonen et al. 2009). The verbal rating scale has five grades (0; no pain, 1; slight pain, 2; moderate pain, 3; severe pain, 4; unbearable pain).

The primary outcome was mean stump pain during the first 5 postoperative days as evaluated once a day at rest by a nurse. Mean outcome was calculated on average for the first 5 days. Other outcomes were stump and phantom pain at 1, 3, and 12 months after the operation assessed by VRS, phantom pain and opioid consumption at 5 postoperative days, and adverse effects (including infections and reoperations). The patients were contacted at 1 month, 3 months, and 12 months by telephone to assess stump pain and phantom pain.

Pain was assessed using NRS in studies III and IV. The NRS is a 11-point scale for patients able to self-report pain, with 0 meaning no pain and 10 the worst imaginable possible pain.

In study IV, the primary outcome was abdominal pain intensity at rest 1 hour after extubation using NRS. Secondary outcomes were abdominal pain and shoulder pain

intensity using NRS at rest at 15 and 30 minutes then every hour, consumption of opioids, and adverse effects (drowsiness, dizziness, nausea, vomiting, and headache) during the hospital stay. Abdominal pain and shoulder pain, adverse effects, consumption of analgesics during the 3 three postoperative days (measured once a day on an electronic questionnaire), overall satisfaction, and length of hospital stay were recorded. Follow-up during the first 3 postoperative days was performed using an electronic questionnaire. Patients who were unable to use e-mail answered on paper forms.

4.4.2 ASSESSMENT OF ANXIETY

Anxiety was assessed using the STAI in study III (Spielberger et al. 1983). STAI is a 40-item questionnaire that evaluates the intensity of state and trait anxiety, both on 20 items. STAI measures general anxiety and is not a pain-specific questionnaire. The score ranges from 20 to 80, with higher scores indicating higher levels of anxiety. Cut-off scores for evaluating anxiety are 20 to 40 (no anxiety to low anxiety), 41 to 60 (moderate anxiety), and 61 to 80 (severe anxiety). STAI form Y was used in study III.

In addition, preoperative anxiety in study III was evaluated using a VAS, which consists of a straight line with the endpoints defining extreme limits (no anxiety at all and anxiety as bad as possible). The patient is asked to mark the anxiety level on the line between the two endpoints. The distance between no anxiety at all and the mark defines the score. The VAS was first introduced in psychology in 1923 (Freyd 1923).

In study IV, anxiety was assessed on NRS with the question “How anxious have you felt during the past week on a scale of 0-10?”.

4.4.3 PAIN TRAJECTORIES

The resolution of pain was described by pain trajectories in study IV. The pain trajectory is a characterization of pain as a curve, normally resolving in intensity over days. It is formed by plotting an individual patient’s pain scores over time. The goal for curve modeling is to estimate the course of acute pain resolution in each individual. Each patient’s trajectory has two features, the initial pain level or the intercept, and the rate of pain resolution or the slope (Chapman et al. 2011, Langford et al. 2011). The rate of acute pain resolution over time is an important clinical outcome that is missed if only static measures of pain are used.

4.5 STATISTICAL ANALYSIS

4.5.1 POWER ANALYSES

In study II, postoperative stump pain as measured by VRS on the first 5 postoperative days was the primary outcome variable. The study group size was decided based on a power calculation, where previous clinical experience revealed the standard deviation of pain on VRS scale (0-4) as 1.0 units. The aim was to be able to detect a clinically meaningful change in pain on VRS on days 1 to 3 after the amputation (reduction of ≥0.5 units, from mean of 3.0 to 2.5). When the alpha error was set to <0.05 and power was set to ≥0.8, at least 63 patients were needed in both intervention groups to be able to detect a statistically significant difference between the groups (two-tailed testing). Considering possible dropouts, the target number of patients was set to 160.

In study IV, pain measured with NRS 60 minutes after surgery was chosen as the primary outcome variable. The study group size was decided based on a power calculation where the standard deviation of pain on NRS was estimated to be 40% of the mean value (sigma 0.4). The aim was to be able to detect clinically meaningful change (reduction ≥30%) in pain. When alpha error was set to <0.05 and the power was set to ≥0.8, at least 28 patients were needed in both intervention groups.

4.5.2 STATISTICAL METHODS

A meta-analysis was planned for study I but was not performed due to heterogeneity of the data. The Cochrane Collaborations bias tool was used to evaluate the risk of bias in the RCTs. The quality of the cohort studies was evaluated according to the applicable GRACE principles.

For study II, all primary and secondary outcomes were analyzed according to the intention-to-treat paradigm. Patient characteristics were compared between groups with Wilcoxon rank-sum test and Fisher's exact test. Stump and phantom pain (evaluated from 0 to 4) were analyzed on each post-operative day and follow-up timepoint separately with ordinal logistic regression. The average pain score over 1 to 5 days was calculated and analyzed with a two-sample *t*-test. For simplicity, means and standard deviations are presented for pain measurements. Daily and cumulative opioid consumption are presented as median and interquartile range (Q1,Q3) and compared with Wilcoxon rank-sum test for 5 postoperative days. All statistical tests were performed as two-tailed with a significance level set at 0.05. The analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

For study III, the worst postoperative MEP and PAR were analyzed using a linear mixed model for repeated measurements. The model included the following factors:

age (as a continuous covariate), gender, expectation of pain (scale of 0 to 3), anxiety measured on VAS, anxiety assessed by STAI Y, chronic pain (yes/no), depression (yes/no), patient's desire for more preoperative information about pain and analgesia (yes/no), analgesic method, prior use of opioids (yes/no), and postoperative time (days 0, 1, and 2). In addition, the interaction with time and opioid use, expectation of pain, need for information on pain, chronic pain, and prior opioid use was examined. Non-significant terms were excluded from the final model. An unstructured covariance structure was used. Square-root transformation was used to fulfill all assumptions for the model. Studentized residuals were used to check assumptions.

All statistical tests were performed as two-tailed with a significance level set at 0.05.

For study IV, to study whether mean change over time differed between the groups in the variables (NRS, abdominal pain), a hierarchical linear mixed model (HLMM) was used including one within-factor (time with 5 timepoints), one between-factor (group), and their interaction. The time factor was handled as categorical to estimate all possible shapes of mean changes over time. Compound symmetry covariance structure was used for time. We also studied in a separate model whether age, gender, BMI, dyspepsia, diagnosis of depression, or the surgeon performing the operation had an effect on the results.

Differences in abdominal pain, nausea, vomiting, headache, and sleepiness between the groups were evaluated at different timepoints with Fisher's exact test.

Opioid consumption in morphine equivalents and time spent in hospital were compared between the groups with one-way analysis of variance.

Normality assumption was assessed visually together with Shapiro Wilk's test. Equality of variances was tested with Levene's test. All statistical tests were performed as two-sided with a significance level set at 0.05. The analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

5 RESULTS

5.1 STUDY SELECTION AND CHARACTERISTICS (STUDY I)

Nineteen studies (9 RCTs, 10 observational studies) with 949 patients were included in the review, which investigated acute pain management after major amputation (Study I). The studies were generally small (11-65 patients), with one exception of an observational study on 198 patients.
The quality of the studies was generally low and the majority were observational studies.
There was extensive variation in the methods, interventions, outcome measures and scales, follow-up periods, data analyses, and reporting of results. This limited the pooling of the results and comparison between studies. The timepoints for measurement of pain intensity also varied between studies. Due to the small number and clinical heterogeneity of the studies, a meta-analysis was not performed.

5.1.1 RESULTS OF INDIVIDUAL STUDIES ON THE REVIEW (STUDY I)

The results of the literature search were divided into the following three groups: epidural analgesia, continuous peripheral local anesthetic infusion, and systemic medications.
Six studies investigated continuous epidural analgesia (Bach et al. 1988, Jahangiri et al. 1994, Karanikolas et al. 2011, Wilson et al. 2008, Yousef et al. 2017, Nikolajsen et al. 1997) and one study compared epidural analgesia and CPI (Lambert et al. 2001). Two out of seven epidural studies reported statistically significantly less pain in the intervention group compared to control group in the first 48 hours; one study compared epidural analgesia to systemic analgesics and one compared to CPI (Karanikolas et al. 2011, Lambert et al. 2001).
Rescue opioid consumption was reported as an outcome in two of the epidural studies at different time points; no differences were observed between the study groups (Nikolajsen et al. 1997, Lambert et al. 2001).
Out of the nine trials that studied CPI (Ayling et al. 2014, Borghi et al. 2010, Elizaga et al. 1994, Fisher et al. 1991, Grant et al. 2008, Malawer et al. 1991, Pinzur et al. 1996, van Geffen et al. 2008, Uhl et al. 2015), one study revealed a decrease in acute

pain at 24 hours (Uhl et al. 2015). Three studies reported a decrease in opioid consumption (Ayling et al. 2014, Fisher et al. 1991, Pinzur et al. 1996).
Three studies assessed systemic analgesics. Gabapentin, ketamine, or memantine did not have an effect on acute postoperative pain after major amputations (Nikolajsen et al. 2006, Hayes et al. 2004, Schley et al. 2007). There were no significant between-group differences in adverse effects on ketamine or gabapentin.
When epidural analgesia was compared to systemic opioid analgesia, there were no significant differences found in motor block, nausea, vomiting, sedation, confusion, or hallucinations. Of the nine studies that investigated the efficacy of CPI, three studies reported catheter failure in 8% to 24% of the patients due to blockage or disconnection. No wound infections related to catheters were reported.

5.2 RECRUITMENT, BASELINE DATA, OUTCOMES, AND ESTIMATION (STUDIES II, III AND IV)

Ninety-three patients were recruited for study II; 91 patients were included in the intention-to-treat algorithm and 89 patients were included in the final analysis. Reasons for dropouts were loss of study papers and study equipment in the first stage and loss of study papers and a catheter detachment during the first hour after the operation in the second stage. Median age (range) was 81 (51-95) years and 44% of the patients were women. Diabetes was present in 38 (42 %) of the patients; 21 were in the CPI group and 17 in the placebo group. There were no clinically significant differences between the groups regarding patient characteristics (Table 3).

Table 3. The patient characteristics of the study groups in study II. The values are expressed in median (range), or by number of patients and percentage. N=91.

	CPI (n=47)	Placebo (n=44)
Age, years	81 (64-95)	82 (51-93)
Gender (female)	20 (43%)	20 (45%)
Diabetes	21 (45%)	17 (39%)
Chronic pain in the leg amputated	32 (70%)	30 (68%)
Other chronic pain	2 (5%)	1 (2%)
Prior opioid medication	24 (51%)	28 (65%)
Prior gabapentinoid medication	10 (21%)	9 (21%)

For study III, 517 elective surgical patients were recruited, of which 516 completed the first and the second questionnaire and were included in the analyses. Of these patients, 199 (39%) were women and median age (range) was 56 (17-83) years. Twelve surgical specialties were included; these were gastric surgery, orthopedics, plastic surgery, urology, endocrine surgery, vascular surgery, gynecology, neurosurgery, ear, nose, and throat surgery, and thoracic surgery. Most operations (38%) were gastric surgery. Thirty-one percent of patients had pre-existing chronic pain. Nine percent of patients received opioid medication preoperatively; this was most common among the orthopedic patients. The STAI-Y evaluation was performed on 492 patients and most (n=429; 87%) reported moderate anxiety (STAI 40-60; mean 45 [SD 3.3]). There were no patients with a high score (STAI 60-80; difficult anxiety). The preoperative expectation of pain was recorded on a four-item scale; 60 (12%) of the patients expected the postoperative pain to be severe, 224 (44%) intensive, 203 (40%) moderate, and 21 (4%) expected no pain after the operation. Details on the surgical procedures, anesthesia, and analgesia are shown in Table 4.

Table 4. Characteristics of the surgical procedures, anesthesia and analgesia in study III. N= 516.

Surgical procedure	N (%)
Major abdominal or gynecological surgery	94 (18%)
Minor abdominal or gynecological surgery	141 (28%)
Thoracic surgery	11 (2%)
Surgery of thyreoidea or neck	42 (8%)
Plastic surgery	64 (13%)
Ear, nose, and throat surgery	34 (7%)
Orthopedics	71 (14%)
Neurosurgery	9 (3%)
Vascular surgery	25 (5%)
Urology	25 (5%)
Anesthesia method	
GA – Inhalation anesthetics	212 (41%)
GA- TIVA	218 (42%)
LA	24 (5%)
GA and epidural	34 (7%)
LA and sedation	28 (5%)
Analgesic method	
Conventional	345 (67%)
Epidural	88 (17%)
Conventional and LA	74 (14%)
PCA	8 (2%)
Hospitalization (days)	2 (0-83)
Day case surgery, 0 days	74 (14%)
1 day	104 (20%)
2 days	108 (21%)
3-5 days	136 (26%)
6-8 days	50 (10%)
>8 days	41 (8%)
Surgical complications	28 (5%)

In study IV, a total of 157 patients were assessed for eligibility and 130 patients were included. Sixty patients in the study group were randomized to receive pregabalin 150 mg or placebo 1 hour preoperatively. Seventy patients in the follow-up group received no intervention. The operation was converted to laparotomy in three cases and these patients were excluded from the final analysis. Twenty-nine patients in the pregabalin group, 30 patients in the placebo group, and 68 patients in the follow-up group (total 127 patients) were included in the analysis. Median (range) age was 48 (19-68) years and 77% were women. Previous or ongoing chronic pain was experienced by 10/29 patients in the pregabalin group, 16/30 patients in the placebo group, and 3/68 patients in the control group (total 29/127 patients; 23%). No significant differences were present between groups in baseline characteristics.

5.3 CHARACTERISTICS OF THE INTERVENTIONS (STUDIES II, III AND IV)

In study II, a total of 70 patients (35 in the CPI group and 35 in the placebo group) received the 72-hour ropivacaine infusion according to the study protocol. In 19 patients the infusion was prematurely discontinued (catheter detachment in 10 cases and protocol misunderstanding in 9 cases).

In study III, conventional analgesia as i.v., i.m., and oral analgesics (NSAIDs), acetaminophen, and opioids were used in 345 cases (67%). In study IV, 60 patients in the study group were randomized to receive pregabalin 150 mg or placebo 1 hour preoperatively. Seventy patients in the follow-up group received no intervention.

5.4 ACUTE POSTOPERATIVE PAIN (STUDIES II, III, AND IV)

After administration of a combination of CPI and a wound infusion of local anesthetic for acute postoperative pain after AKA (Study II), the mean (SD) intensity of stump pain during the first 5 postoperative days as assessed by VRS was 1.4 (0.8) in the CPI group and 1.9 (0.9) in the placebo group (P=0.006). On the first postoperative day, mean (SD) pain was 1.7 (1.3) in the CPI group and 2.3 (1.2) in the placebo group (P=0.04). The mean (SD) intensity of phantom pain on the first postoperative day was 0.8 (0.9) in the CPI group and 0.9 (1.1) in the placebo group (P=0.80). Details on stump pain, see Table 5.

Table 5. Stump pain on VRS in study II. Values are expressed as mean (standard deviation).

	CPI	Placebo	*P*-value
Days 1-5 (N=87)	1.4 (0.9)	1.9 (0.9)	0.006
Day 1 (N=79)	1.7 (1.3)	2.3 (1.2)	0.04
Day 2 (N=78)	1.5 (1.2)	1.9 (1.1)	0.16
Day 3 (N=73)	1.5 (1.0)	1.5 (1.0)	0.27
Day 4 (N=70)	1.2 (1.2)	1.5 (1.0)	0.31
Day 5 (N=71)	1.3 (1.2)	1.5 (1.1)	0.29
1 month (N=49)	0.7 (0.8)	0.8 (1.2)	0.63
3 months (N=44)	0.4 (0.9)	0.2 (0.6)	0.52
12 months (N=30)	0.8 (1.4)	0.7 (1.0)	0.54

Ten out of 89 (11%) of the patients were unable to evaluate their stump pain and 13/89 (15%) were unable to evaluate phantom pain on the first postoperative day.
In the observational study on elective surgical patients (study III), the worst PAR during first 48 hours postoperatively was severe (NRS 6-10) in 221 (43%) of the patients and moderate (NRS 4-5) in 109 (16%) patients. The worst MEP during two days was severe in 238 (48%) of the patients and moderate in 121 (24%) of the patients.
In study IV, the majority of the patients did not experience severe pain (NRS ≥6). However, despite pain treatment with i.v. opioids given repeatedly as needed, 46/127 (36%) patients had severe pain (NRS ≥6) at some time during the 3 hours of postoperative care. Of these patients, 9 (31%) were in the pregabalin group, 16 (53%) in the placebo group, and 21 (31%) in the follow-up group. Shoulder pain intensity was low throughout follow up. For details on postoperative abdominal pain, see Table 6.

Table 6. Abdominal pain in recovery room as assessed by NRS in study IV. Values are expressed as mean (standard deviation). The P-value describes group differences between the three groups at each timepoint.

	Pregabalin (N=29)	Placebo (N=30)	Follow-up (N=68)	*P*-value
15 min	4.2 (2.5)	4.5 (2.7)	3.5 (2.6)	0.12
30 min	3.8 (2.5)	4.5 (2.6)	3.6 (2.3)	0.14
1 hour	3.5 (2.2)	4.0 (2.2)	3.3 (2.1)	0.31
2 hours	2.8 (2.2)	2.8 (2.3)	2.3 (1.8)	0.56
3 hours	2.6 (1.9)	2.4 (1.8)	1.8 (1.2)	0.31
4 hours	2.1 (1.9)	2.9 (2.8)	1.8 (1.4)	0.16

5.5 CONSUMPTION OF ANALGESICS (STUDIES II AND IV)

In study II, the opioid consumption on the first postoperative day was 3.3 (1.1-7.8) in the CPI group and 5.0 (2.8-13.9) in the placebo group in mg i.v. morphine equivalents, median (range), P=0.03. The total amount of opioid required during the first five postoperative days was 11 (0,4,24,87) in the CPI group and 16 (0,10,29,124) in the placebo group, in mg i.v. morphine equivalents, median (minimum, lower and upper quartile and maximum), P=0.12. For details on opioid consumption, see Table 7.

Table 7. Opioid consumption in mg i.v. morphin equivalents on first five postoperative days in study II. Daily values are expressed as median (range). In the total amount median (minimum, lower and upper quartile and maximum) are given.

Postoperative day	CPI (N=47)	Placebo (N=42)	*P*-value
1. (N=89)	3.3 (1.1-7.8)	5.0 (2.8-13.9)	0.03
2. (N=89)	2.2 (0-5.6)	3.3 (1.1-4.4)	0.40
3. (N=89)	1.1 (0-3.3)	1.1 (0-3.3)	0.98
4. (N=89)	1.1 (0-2.2)	1.1 (0-3.9)	0.13
5. (N=89)	1.1 (0-3.3)	1.1 (0-2.2)	0.89
Total amount	11 (0,4,24,87)	16 (0,10,29,124)	0.12

In study IV, opioid consumption expressed as median (range) i.v. morphine equivalents during the first hour was 8.8 (5.0-10.0) mg in the pregabalin group, 10.0 (5.0-10.0) mg in the placebo group, and 5.0 (0-10.0) mg in the follow-up group (P=0.07). The total opioid consumption during the hospital stay was 10.0 (5.0-15.0) mg in the pregabalin group, 10.0 (5.0-15.0) mg in the placebo group, and 10.0 (0-15.0) mg in the follow-up group (P=0.14). Paracetamol 1 g orally was given to 102 patients. Tramadol 50 mg orally was given to 58 patients. Twenty-five (20%) of the operated patients did not need any analgesics during the hospital stay.

5.6 ADVERSE EFFECTS (STUDIES II, III, AND IV)

In study II, six catheters in the placebo group and none in the CPI group were detached prematurely after AKA (Study II). There was one reoperation and one wound infection in the placebo group. Two patients died on the second postoperative day and both were in the placebo group.
In study III, 44% of the patients reported having no side effects from the analgesics and 54% reported some side effects.
In study IV, after receiving a single dose of pregabalin 150 mg 1 hour before the operation, patients in the intervention group did not experience more adverse effects than those in the placebo or follow-up group.

5.7 PERSISTENT PAIN (STUDIES II AND IV)

In study II, there were no differences between groups in the intensity of stump pain or phantom pain during the 12-month follow-up after AKA. The intensity of stump and phantom pain was generally low. At 12 months, the mean (SD) intensity of stump pain was 0.8 (1.4) and 0.7 (1.0) in the CPI and placebo groups, respectively (*P*=0.54). The mean (SD) intensity of phantom pain at 12 months was 1.3 (1.4) and 1.6 (1.0) in the CPI and placebo groups, respectively (*P*=0.51).
In study IV, 87% of the patients (111) answered the postoperative electronic questionnaire during the three postoperative days of follow up after day-case cholecystectomy. The highest mean (SD) abdominal pain intensities for the pregabalin, placebo, and follow-up groups for day 1 were 3.4 (2.5), 4.0 (2.5), and 2.9 (SD 1.6); 2.7 (1.9), 3.5 (2.1), and 2.3 (SD 1.0) for day 2; and 2.2 (SD 1.8), 2.6 (SD 2.0), and 1.5 (SD 1.3) for day 3, respectively (*P*=0.067).
One month after surgery, 84 (66%) patients answered the electronic questionnaire. The intensity of abdominal pain as assessed by NRS was 0.3 (SD 0.6) in the pregabalin group, 0 (SD 0.7) in the placebo group, and 0.1 (SD 0.4) in the control group (*P*=0.067).

5.8 LENGTH OF HOSPITAL STAY (STUDIES II, III, AND IV)

In study II, the length of hospital stay after AKAs varied between different study centers according to their protocols for postoperative care. In some study centers, the aim was to transfer the patient to a secondary hospital on the first postoperative day. Nine patients were transferred on the first postoperative day; 19 patients on the second and a total of 57 patients were transferred during the first 5 postoperative days. There were no differences between the groups in the total length of hospital stay.

Among elective surgical patients in study III, the duration of hospitalization ranged from 0 to 83 days. Fourteen percent of the patients went through day-case surgery and were discharged on the day of operation; 41% spent 1 to 2 days in the hospital, 26% 3 to 5 days, 10% 6 to 8 days, and 8% over 8 days.

The administration of pregabalin did not lead to prolonged hospital stay after day-case cholecystectomy in study IV. Mean (SD) duration of hospitalization was 275 (69) minutes in the pregabalin group (4 hours and 35 minutes), 250 (61) minutes in the placebo group (4 hours 10 minutes), and 266 (70) minutes in the follow-up group (4 hours 26 minutes) (P=0.44).

5.9 LONG-TERM OUTCOMES (STUDY II)

In study II, 54% (48) patients died and 6% (5) were lost to follow up during the 12-month follow-up period. Of the 36 patients who were contacted at 12 months after the operation, 28 (78%) had returned to their prior residence and 8 (22%) moved to a nursing home.

5.10 ASSOCIATIONS BETWEEN PREOPERATIVE FACTORS AND POSTOPERATIVE PAIN (STUDIES III AND IV)

In study III, an association was observed between the worst postoperative MEP and expectation of pain (P=0.043), chronic pain (P=0.006), younger age (P<0.0001), and preoperative opioid use (P=0.040). There was also an association between the experience of being preoperatively inadequately informed about pain and pain management and postoperative pain (P<0.0001). See Figure 3 for details of the association between the expectation of pain and worst postoperative MEP during two postoperative days.

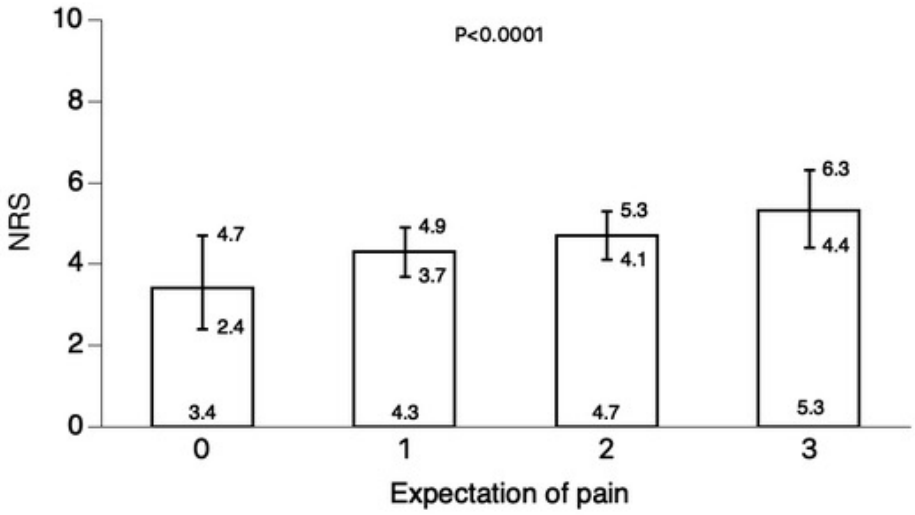

Figure 3. Association between the preoperative expectation of pain and worst postoperative MEP in study III. The expectation is expressed as 0-no pain, 1-moderate pain, 2-intensive pain, 3-severe pain. Pain values are expressed as mean (standard deviation).

The resolution of worst acute postoperative MEP (P=0.018) and PAR (P=0.040) was slower in the group of patients with a high preoperative expectation of pain than in patients with a lower pain expectation (Figure 4a and 4b). In addition, prior use of opioids led to slower resolution of postoperative pain (P=0.001).

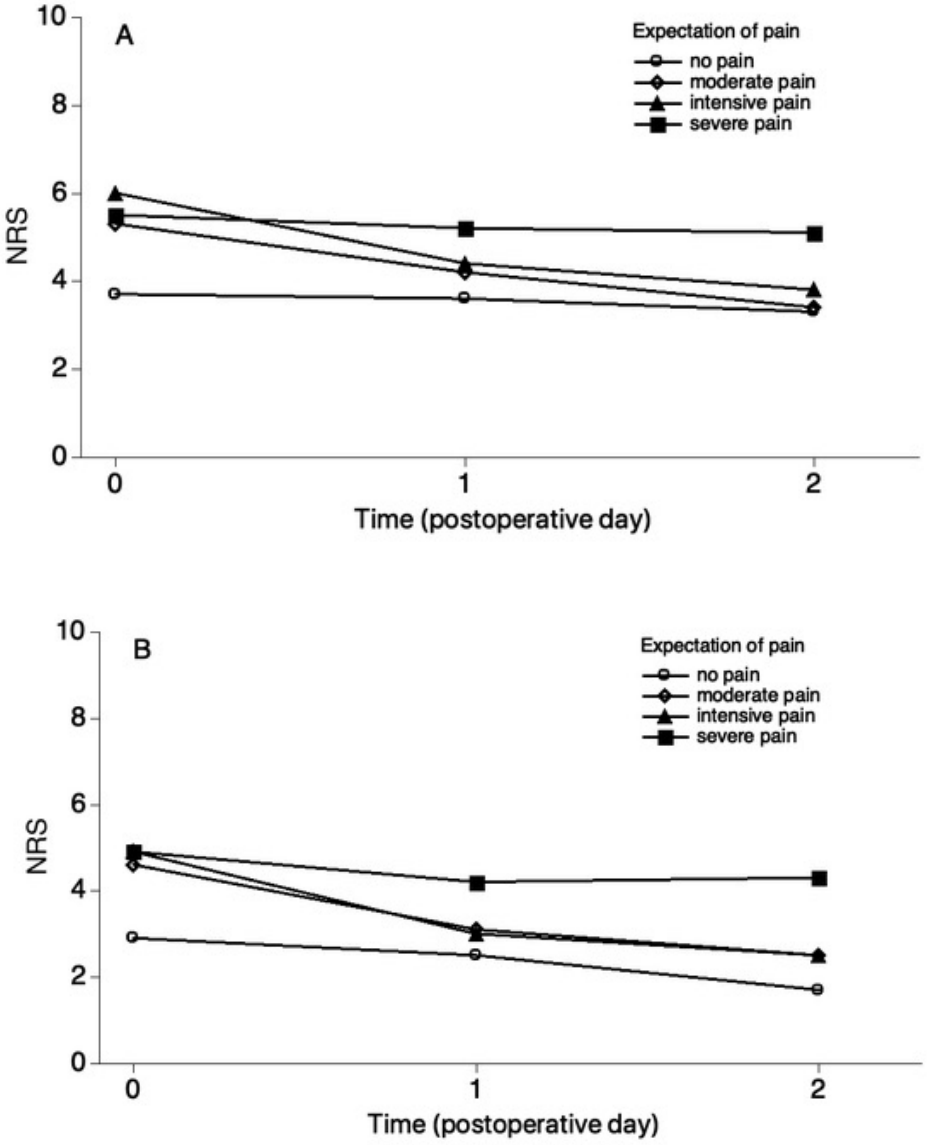

Figure 4. The resolution of pain on the first two postoperative days for patient groups expecting no or moderate, intensive, or severe postoperative pain. Pain values are expressed as mean. A; mean MEP, B; mean PAR.

There was no association between postoperative pain and gender (P=0.123), anxiety on STAI Y form (P=0.547) and anxiety reported on VAS (P=0.054), diagnosed depression (P=0.617), BMI, ASA classification, surgical specialty, fear of postoperative pain, and the expectation of analgesic effectiveness.

In study IV, the question on anxiety as assessed by NRS “How anxious have you felt during the past week on a scale of 0-10?” predicted higher postoperative pain intensity in a linear manner. Anxiety was positively associated with postoperative abdominal pain intensity during the 4 hours in the recovery room (P=0.04). Chronic pain, previous experiences of severe pain after surgery, expectation of high intensity of postoperative pain, and expectation of a large amount of pain medication needed was not associated with postoperative pain. Thus, the five-item questionnaire used in this study did not predict postoperative pain.

6 DISCUSSION

6.1 MAIN FINDINGS

The main finding of the systematic review on the management of acute pain after major amputations is that there are only a few small clinically heterogenous studies on the topic and most studies are observational. Only nine RCTs were found. The quality of the RCTs were evaluated by the criteria described in the Cochrane risk of bias assessment tool (Higgins et al. 2011) and the overall study quality was generally low. The results concerning acute pain originate mainly from studies in which acute pain was not the primary outcome. The 19 studies included in the review were heterogenous in terms of study interventions, methodology, outcomes and reporting and most were not randomized. On the basis of these facts we decided not to perform a meta-analysis.

The main finding of our RCT on postoperative pain treatment with a combination of an ischiatic perineural and local wound anesthetic infusion is that this method decreases acute stump pain during the first five postoperative days and opioid consumption on the first postoperative day after AKA compared with placebo. This approach does not seem to decrease the incidence or intensity of chronic pain after AKA.

In our prospective study on surgical patients, the main finding is that preoperative expectation of pain, younger age, chronic pain, and prior use of opioid analgesics had a correlation with acute postoperative pain in patients going through various elective surgical procedures from 12 different specialties. Anxiety or diagnosed depression did not correlate with postoperative pain in this population. A considerable proportion of patients (43%) expected to have severe pain after surgery and the expectation of pain was associated with the postoperative pain experienced (P=0.043). One third (33%) of the patients were afraid of postoperative pain and 9% expected the effect of analgesics to be only fair. The experience of inadequate preoperative information on postoperative pain and pain management was associated with postoperative pain.

The main finding of the randomized controlled multi-arm parallel study on targeted preoperative adjuvant pain medication on day-case laparoscopic cholecystectomy was that preoperative pregabalin 150 mg did not decrease pain intensity after

laparoscopic day-case cholecystectomy compared with placebo when administered targeted to patients with more risk factors for postoperative pain according to a short systematic preoperative risk assessment. Despite immediate postoperative opioid treatment, 36% of the cholecystectomy patients experienced severe (NRS ≥ 6) postoperative pain during the first hours. The preoperative state of anxiety on VAS was associated with postoperative pain intensity.

6.2 POSTOPERATIVE PAIN AFTER AMPUTATIONS

Although vascular surgery techniques have developed in recent last years, amputations are still a common procedure among patients suffering from peripheral vascular disease. However, as concluded in the review and highlighted by others, there is minimal data to support the choice of postoperative analgesia (Geertzen et al. 2015, Schug et al. 2015, Halbert et al. 2002). In studies that report rescue opioid consumption, the amount of rescue opioid administered in the first 72 hours indicated that postoperative pain following major limb amputations is severe. There is also a wide range of opioid use in the included studies. Elderly patients are especially vulnerable to opioid-related adverse effects and there is a genuine need for interventions that could decrease postoperative opioid consumption.

6.2.1 EPIDURAL ANALGESIA

Although strong evidence is lacking, data from four RCTs and two observational studies with a total of 257 patients indicate that epidural analgesia may be effective in decreasing the intensity of stump and phantom pain during the first postoperative days. In addition, there was no difference in the consumption of rescue opioids during the first 72 hours after the operation between epidural and placebo groups. Epidural analgesia seems to be effective and safe in amputee patients, but the widespread use of long-acting anticoagulant medication in atherosclerosis often prevents the use of this technique. This is because the washout period of the anticoagulant may be up to 1 week before the epidural can be safely inserted; the decision to amputate is made quickly; and surgery must often be performed in the upcoming days due to pain and ischemia. It is also noteworthy that the failure rate of epidural analgesia is up to 30% in clinical practice (Hermanides et al. 2012). In addition, in some centers the patients are discharged to secondary hospitals in a very acute phase after amputation; in these hospitals the use of epidural analgesia is not possible due to lack of expertise and resources. This in turn may prevent the use of epidural analgesia. The reason for early discharge is financial. Early discharge can be considered if it is ethically justified to move a patient to a hospital where the care

might otherwise be good but where the best available pain management method is not available.

There is minimal data on systemic analgesics in acute pain after amputations. Two recent reviews concluded that there is a lack of firm evidence on the benefit of gabapentin and pregabalin as a part of multimodal postoperative analgesia (Fabritius et al. 2016, Fabritius et al. 2017). It is noteworthy that pregabalin can increase the risk of respiratory depression and negative cognitive effects when combined with opioids (Myhre et al. 2016, Savelloni et al. 2017). This risk should be considered in postoperative use especially in elderly patients. The routine use of gabapentinoids for postamputation pain is probably not advisable, but it may be beneficial in some patients after careful consideration. According to a recent Cochrane Database systematic review, ketamine in mixed surgery is effective in reducing opioid requirements and pain scores in the first 24 hours after surgery in subanesthetic bolus doses of 0.25 to 1 mg and infusions of 2 to 5 µg/kg/minute of racemic ketamine (Brinck et al. 2018). Based on the data from other types of surgery, ketamine could be a suitable adjuvant in the treatment of pain after major amputations.

6.2.2 CPI AND CONTINUOUS WOUND INFILTRATIONS

CPI of local anesthetic and single-shot nerve blocks have been widely investigated in surgery types other than amputations (such as major knee surgery including knee arthroplasty and shoulder surgery). There is firm evidence that these techniques decrease the intensity of postoperative pain and consumption of postoperative opioids (Chan et al. 2014, Li et al. 2016, Xu et al. 2014, Mudumbai et al. 2014, Richman et al. 2006, Bingham et al. 2012). Recent studies on the effect of continuous perineural femoral infusion (Chan et al. 2014) and the combination of a femoral nerve block and a sciatic nerve block (Li et al. 2016) after major knee surgery warrant attention when planning the future studies and treatment options for acute pain after amputations.

Continuous wound infiltrations with local anesthetics have been widely studied. According to a recent Cochrane Database systematic review of six studies on continuous local anesthetic wound infusion for postoperative pain after midline laparotomy for colorectal resection in adults, continuous wound infusion of a local anesthetic compared with placebo reduces postoperative PAR and length of hospital stay (Liang et al. 2019). Based on another review, wound infusions do not seem to reduce opioid consumption or acute pain after different surgery types (Gupta et al. 2011). In major amputations, continuous perineural local anesthetic infusion is a technique that may be considered as in between a nerve block and a wound infusion; the catheter is placed in the wound area distal to the injured nerve and is usually placed into the nerve sheath or next to the nerve. The different nerves targeted with

the continuous infusion are the sciatic nerve in AKA and the common peroneal nerve or tibial nerve in BKA.

Based on the limited data from the non-randomized observational studies included in the review, CPI seems to decrease opioid consumption of amputee patients in the first postoperative 72 hours. There was only one prior RCT with a total of 21 patients that investigated CPI compared with placebo. The results of this underpowered trial revealed that opioid consumption of the first 2 postoperative days was decreased in patients treated with CPI of the sciatic nerve for 72 hours with 0.5% bupivacaine 1 ml/h compared with a saline infusion. Considering that this method has been in a routine clinical use for several years in some centers, it is quite surprising that this is the only prior RCT on the topic.

Our RCT on CPI combined with wound infusion revealed that this technique of two catheters administering a continuous local anesthetic infusion to the perineural space of the ischiatic nerve and to the wound area for 72 hours diminishes opioid consumption on the first postoperative day and acute stump pain throughout the entire follow-up period of 5 postoperative days. Our study did not reveal an effect on acute phantom pain.

Our study also showed that CPI combined with wound infusion diminishes pain and the need for opioids and may decrease the risk of adverse effects in elderly and fragile patients undergoing amputation. Reducing pain and opioid consumption would most likely accelerate healing and lower the risk of complications and persistent pain. It is noteworthy that the reduction of postoperative opioid consumption was rather low in our study. Whether CPI is as effective as epidural or a combination of other types of nerve blocks remains unclear and would be interesting to investigate in the future. It is quite surprising that a catheter inserted in a retrograde manner from the distal end of the dissected nerve can offer good analgesia. This might be due to spreading of the local anesthetic further to the nerve sheath causing analgesia. Thus, it is worth considering to place the catheter as deep as possible into the dissected nerve sheet.

A noteworthy problem in the utilization of a perineural catheter is device detachment. Careful attention should be given to catheter attachment to ensure continuity of the infusion. Taping or sewing the catheter carefully on the skin, taking the catheter outlet sufficiently far from the wound, and inserting the catheter deep enough to the perineural space may help keep the catheter in place. When dissecting the nerve, the remaining part should be attached with a surgical instrument to prevent it from withdrawing inside to the residual limb. The efficacy of this technique is affected by the fact that the catheter might be placed into the adjacent tissue instead of the nerve sheet and that it can detach easily. It is also noteworthy that the technique has to be feasible regarding insertion and remaining in place for a sufficient period of time. Based on our clinical experience, catheter detachment occurs coincidentally

and is not associated with any specific catheter type. In our study, an instructional video for the insertion of the perineural catheter was made for the centers participating in the study of CPI in amputations. This video is now available as educational material for surgeons conducting and students training in AKA.

6.2.3 DIABETES AND POSTOPERATIVE PAIN AFTER AMPUTATION

In our study, diabetes was present in 38 (42 %) of the patients, 21 in the CPI group and 17 in the placebo group. Neuropathy, or damage of the nerves of the peripheral nervous system is common in these patients, the incidence being 30-50 % (Callaghan et al. 2012). The symmetrical symptoms of neuropathy typically begin in the feet and spread proximally in time. The symptoms include numbness, pain, tingling sensations and weakness. Which symptom predominates varies from patient to patient, and the neuropathy may thereby cause difficult neuropathic pain, or on the other hand a totally painless situation despite of a significant ischemic disease. It has been studied, how the peripheral neuropathy affects the manifestation of an ultrasound-guided popliteal sciatic nerve block. According to Baeriswyl et al., patients with diabetic peripheral neuropathy demonstrated reduced time to onset of sensory blockade, with increased time to first opioid request when compared with patients without neuropathy (Baeriswyl et al. 2018). In our study, there was no significant difference between the groups concerning diabetes, but the fact that diabetic neuropathy causes a variety of symptoms from neuropathic pain to total numbness may have had an effect on our results.

6.2.4 PHANTOM PAIN

Phantom pain is a painful sensation perceived in the missing limb after amputation (Merskey et al. 1994). It is distinct from stump pain, which is pain in the residual body part and is common immediately after the operation. Stump pain usually diminishes with wound healing but may also persist and increase over time (Nikolajsen et al. 1997, Jensen et al. 2000, Whyte et al. 2001). Also phantom pain usually diminishes over time, usually within the first year after amputation, but it may also persist and increase in intensity (Habert at al. 2002). Phantom limb sensation is any sensation as paresthesia or dysesthesia of the missing body part. According to earlier studies, the incidence of phantom pain after major limb amputations is 80%, of which 75% develops during the first postoperative days (Nikolajsen et al. 1997).

The number of studies that have investigated chronic pain after amputation and especially chronic phantom pain is large compared with the number of studies on acute pain after amputation. The phenomenon of phantom pain is unique and has

encouraged research. However, despite dozens of studies on the topic, no effective analgesic for chronic phantom pain has been found (Halbert et al. 2002). This also encourages intensive acute pain management after amputations to avoid the chronification of postsurgical pain.
In contrast to previous studies, in our study the intensity and incidence of phantom pain was low both in the acute phase and in the 12-month follow-up period in both CPI and placebo groups. At 12 months, 19 (53%) of the patients contacted reported phantom pain. Only 6 patients (17%) had moderate to severe pain (VRS ≥4) and most had mild pain. The incidence and intensity of stump and phantom pain observed in the current study are lower than in previous studies on major amputations. This might be due to the attempts of enhancing the pain management of the acute postoperative period. The long-term outcomes on pain did not differ between the intervention and placebo groups.

6.2.5 PREOPERATIVE PAIN

Nearly all patients scheduled for amputation experience acute or chronic pain before the operation. Preoperative pain and severe acute postoperative pain might increase the risk for persistent postoperative pain and increased opioid consumption (Hanley et al. 2007, Kalkman et al. 2003, Bisgaard et al. 2005, Kehlet et al. 2006, Janssen et al. 2008, Fletcher et al. 2015). Some studies have shown a correlation between the level of pain preceding amputation and chronic pain after amputation. It has been suggested that adequate analgesia before amputation and in the acute phase after amputation could prevent chronic pain (Nikolajsen et al. 1997, Nikolajsen et al. 2012). No firm conclusions on prevention of chronic pain can be drawn based on our review or from the RCT on CPI. Further studies are thus warranted on this topic. In the future also genetic studies may also bring new aspects to acute and chronic pain after amputations.

6.2.6 STUDYING ELDERLY PATIENTS

Studying elderly patients undergoing amputations is challenging. Dementia, postoperative confusion, and delirium are common in these patients, making evaluation of pain and drug effects difficult. However, treatment of pain should be improved in this vulnerable patient group. The proportion of elderly patients is growing, and there is a need for future studies on pain management after surgery in this population.
One problem in studying this population is informed consent and ethical approval of studies on elderly patients if dementia and cognitive impairment are present. For the RCT on CPI, we received an approval from the local ethical board even though it

was assumed that most of the patients would suffer from dementia. We justified the study with the fact that postoperative pain management in elderly patients has not been studied extensively and that both groups in the study would receive the best pain management available. Our study was conducted by administering an effective ropivacaine dose for both groups at the end of surgery, thus ensuring effective analgesia in the very acute phase. However, this might have also affected the postoperative pain results. Another problem in conducting studies on the elderly is the assessment of postoperative pain. Possible dementia and cognitive impairment are usually exacerbated in the postoperative period, which accordingly makes the evaluation of postoperative pain, response to analgesics, and adverse effects difficult. The same factors that make studying this patient group difficult also make pain management difficult. There are good pain assessment methods developed for the elderly and patients with cognitive impairments, such as the PAINAD (Pain Assessment in Advanced Dementia Scale) evaluation (Warden et al. 2003), which has also been translated to Finnish. However, use of the PAINAD evaluation is limited in the postoperative period, because it is developed to situations where the nurses are familiar with the patients individual features for a longer period of time. Progress in acute pain management requires effective pain assessment. Currently, work is being done to improve routine documentation of pain in surgical wards.

6.3 RISK FACTORS OF POSTOPERATIVE PAIN

Risk factors for postoperative pain have been under investigation since the observation that postoperative pain intensity does not depend solely on the procedure performed. Although several studies on the topic have been published, few have investigated the possibilities of improving postoperative pain management by considering individual risk factors.

In our observational study of 516 surgical patients, preoperative expectation of pain, younger age, chronic pain, and prior use of opioid analgesics correlated with acute postoperative pain in mixed elective surgery. Anxiety or diagnosed depression did not correlate with postoperative pain in this population.

6.3.1 PREOPERATIVE EXPECTATION OF PAIN

The resolution of pain was slower in patients with a high preoperative expectation of pain than in those with a lower pain expectation. The slower resolution of acute postoperative pain is associated with persistent postoperative pain in some studies. This has been recognized as an important factor in the early diagnosis of persistent postoperative pain (Pagé et al. 2016). This suggests that patients with high pain expectancy are also at higher risk of developing persistent pain. Previous studies

have shown that the expectation of pain is associated with postoperative acute pain after breast surgery and after cesarean section (Gramke et al. 2009, Mamie et al. 2004, Sipilä et al. 2017, Katz et al. 2005, Montgomery et al. 2004, Montgomery et al. 2010, Pan et al. 2013, Sommer et al. 2010, Booth et al. 2016).

6.3.2 YOUNGER AGE

Younger age is associated with postoperative pain in our study and it seems to be one of the strongest predictors of postoperative pain also according to previous studies (Ip 2009, Yang 2019, Chung et al. 1997, Kalkman et al. 2003, Gagliese et al. 2008, Bisgaard et al. 2001, Caumo et al. 2002, Lau et al. 2004). Converse findings, however, have been reported (Healey et al. 1998, Rudin et al. 2008, Chia et al. 2002, De Cosmo et al. 2008, Mamie et al. 2004, Munafo et al. 2003). It is noteworthy, that younger age which seems to predict postoperative pain in most studies and is considered a reliable risk factor for postoperative pain, does not seem to predict pain in other studies. This seems to be the case concerning the studies on risk factors in general. It may be, that there are individual protective factors that contribute to the risk of postoperative pain. These factors have not yet been widely studied but are of interest in future studies.

6.3.3 CHRONIC PAIN

Prior chronic pain and use of opioids predicted acute postoperative pain. Although similar findings have been reported previously (Ip et al. 2009, Caumo et al. 2002), converse findings have also been reported (Yang et al. 2019). In our study, chronic pain and prior use of opioids were most common among patients undergoing spinal surgery of the lumbar or cervical region. In these patients, surgery does not always have an anticipatory effect on pain. According to studies on lumbar laminectomies, over half of the patients had an opioid medication preoperatively. Of these, 16% continued opioid use 12 months after the operation, which indicates persistent postoperative pain (Khan et al. 2019, Wright et al. 2019).

6.3.4 ANXIETY

Despite having a predictive value in some prior studies (Yang et al. 2019, Ip et al. 2009, Pan et al. 2006, Pan et al. 2013, Booth et al. 2016, Sipilä et al. 2017), anxiety did not predict acute pain in our study. This is most likely due the fact that anxiety scores were low in this study population (mean STAI 45 [SD 3.3]; mean VAS 28 [SD 26]). The predictive value of anxiety is more likely to be present in patients with a higher score indicating more severe anxiety (STAI 60-80). Of the measures of

anxiety, VAS is of greater interest in our study as it could be added to a short preoperative evaluation; STAI consists of 40 questions and is not useful as a screening tool in a clinical preoperative situation. The six-item State-Trait Anxiety Inventory (STAI-6) (Marteau et al. 1992) seems to have fairly good capability in screening anxiety, but its ability to detect the risk of postoperative pain has not been studied.

It is noteworthy that most patients (56%) expected to have moderate or severe pain after surgery; 33% of the patients reported fear of upcoming postoperative pain; and 9% of the patients expected the effect of analgesics to be weak at most. Since the actual postoperative pain levels are much lower and the effect of analgesics are mostly good, adequate preoperative information on pain and pain management could assist in preparing the patients for the upcoming surgical procedure and thus prevent fear of severe postoperative pain and inadequate analgesia after surgery. These factors affect the actual postoperative pain experienced and should be considered particularly if anxiety is present. Similar findings have also been previously reported (Powell et al. 2016), although more studies are necessary to investigate the effects of different preoperative interventions to reduce fear and expectation of pain.

6.3.5 THE ROLE OF PREOPERATIVE INFORMATION ON PAIN AND PAIN MANAGEMENT

Our study emphasizes the crucial role of providing adequate preoperative information. The patient's experience of inadequate preoperative information on postoperative pain and pain management had a strong association with postoperative pain. An international cohort study of over 16 000 European patients also revealed that satisfaction with postoperative pain treatment is associated with participation in pain treatment decisions and the impression of appropriateness of pain treatment and care combined with information on analgesia (Schwenkglenks et al. 2014). As a novel aspect, we studied from whom the patients expected to receive information and from whom they actually received information on pain and pain management. Most patients expected to receive the most information from the operating surgeon before the operation, but instead information was provided in most cases by a nurse in the surgical ward after the operation.

6.3.6 STUDYING THE RISK FACTORS OF POSTOPERATIVE PAIN

There are some aspects that should be considered when studying risk factors for postoperative pain. One is the somewhat misconceived assumption that surgery will diminish pain. This is not always the case, as is often seen for example in spinal surgery or in total knee replacement. Surgery is often performed for relative

indications in a situation where pain is not always present in the preoperative state. According to some studies, as much as 30% of patients undergoing laparoscopic cholecystectomy continue to have upper abdominal pain after the operation. It is hypothesized that if gallstones were the reason for the pain in the first place, then the persistent postoperative pain is caused by something else that was already present before the operation. Surgery can also be the origin of persistent postoperative pain. This is observed for example in cosmetic surgery, where after a completely painless situation the patient may suffer from persistent postoperative pain that can in some cases be severe. These facts inevitably constitute significant bias in all studies on preoperative risk factors for postoperative pain. An ideal situation for a study on risk factors would be a standard operative procedure that in most cases clearly diminishes pain in the area operated.
Overall, there are many factors that cause bias in studies on risk factors. Therefore, register studies with large patient populations may yield more reliable results. In addition to the psychological risk factors for pain, there may be protective factors such as resilience, different coping methods, and different personality traits. These factors have not been studied extensively.

6.4 PREOPERATIVE TARGETING OF ADJUVANT ANALGESICS

To our knowledge, our study on targeting preoperative adjuvant pregabalin medication was the first trial on the effect of a preventive adjuvant analgesic targeted to a preselected group of patients based on individual risk factors in day-case surgery. We applied three predictive questions formerly validated in two cesarean section studies (Pan et al. 2013, Booth et al. 2016) and combined one question on chronic pain and one on intensive pain after earlier surgery.
Consistent with previous studies on cesarean section patients (Pan et al. 2013, Booth et al. 2016), preoperative anxiety had a positive correlation with postoperative pain. However, in contrast to these studies, expectation of either postoperative pain intensity or amount of analgesic needed, chronic pain, or the preoperative pain in the area to be operated did not correlate with postoperative pain. The fact that up to 30% of patients continue to have similar preoperative pain symptoms after cholecystectomy probably explains this result. From this perspective, laparoscopic cholecystectomy is not the best example for studying risk factors for postoperative pain, as preoperative pain may be nonspecific and persist after surgery.
Our trial showed that there is a group of patients that experience severe pain during the first postoperative hours after laparoscopic cholecystectomy even when multimodal analgesia is administered and opioids are offered as needed. A similar finding was reported in an earlier trial of day-case hallux valgus surgery (Mattila et

al. 2010). This emphasizes the need for preventive pain management based on individual risk assessment of the surgical patient. This need has also been emphasized in the Clinical Practice Guideline from the American Pain Society (Chou et al. 2016). It is noteworthy that intensive acute post-surgical pain is considered a risk factor for chronic pain in some studies (Althaus et al. 2014). As chronic pain is difficult to treat, every effort should be made to reduce the risk of chronification of postoperative pain.

Preoperative pregabalin administered in a targeted way did not increase side effects or prolong hospital stay in our study. However, it is noteworthy that pregabalin can increase the risk of respiratory depression and negative cognitive effects when combined with opioids. This should be considered in postoperative use particularly in day-case surgery (Myhre et al. 2016). Previous RCTs and a single meta-analysis revealed that preoperative pregabalin decreases postoperative pain and opioid consumption after laparoscopic cholecystectomy (Bockbrader et al. 2010, Agarwal et al. 2008, Balaban et al. 2012, Zhang et al. 2011, Li et al. 2017). However, two meta-analyses suggest that firm evidence for the use of gabapentinoids in postoperative pain management is lacking (Fabritius et al. 2016, Fabritius et al. 2017). It is noteworthy that in these studies, gabapentinoids were administered based on the type of surgery and were not stratified and targeted based on the patient's individual risk factors for postoperative pain. This is generally the case in all studies on postoperative pain management thus far. Such studies are designed solely based on the surgical procedure and patients are not stratified according to the already extensively studied risk factors for postoperative pain. Accordingly, studies focused on individually targeted pain management are warranted.

6.5 METHODOLOGICAL CONSIDERATIONS

A systematic review is an overview of all available evidence concerning a particular research question. To improve the reporting and quality of systematic reviews the PRISMA statement guideline is recommended. This is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. The Cochrane Bias Tool is a method created to strengthen the value of systematic reviews by systematically evaluating the quality of the individual studies on the topic. The strength of the review can further be improved with a meta-analysis. However, the rationale must be considered, and if the individual studies are very heterogenous, the meta-analysis should not be performed.

In clinical studies on postoperative pain management, randomized controlled trials are known to provide the most reliable evidence of an intervention. However, if the performance and reporting is inadequate, readers are unable to judge the validity and reliability of the trials. The CONSORT statement is an evidence-based minimum set

of recommendations that describe good practice guidelines for reporting randomized trials.
The goal of an observational study is to identify and evaluate causes or risk factors of health-related events. The STROBE statement is an evidence-based guideline to facilitate the reporting of observational studies.
In the evaluation of pain, subjective pain rating scales such as NRS, VAS, and VRS are widely used. The advantage of the VRS is, that it also seems to be suitable also for the cognitively impaired. These rating scales are highly subjective and thus secondary outcome measures such as functional assessment and analgesic consumption preferably on PCA should be considered.
Study IV has a somewhat distinct study design. A predictive tool to assess the patients' risk for postoperative pain was created and was used as a basis for targeting the study intervention. A methodological weakness of this study is that the questionnaire that was designed based on prior studies on risk factors was not tested before the study. Overall, this questionnaire did not predict postoperative pain in day-case cholecystectomy, even when the individual questions in the questionnaire were reported to be predictive in prior studies on various surgery.

6.6 LIMITATIONS OF THE STUDY

There are some limitations in this thesis that may affect the results. Prior data on acute pain management after major amputation are very limited, which in turn affects the results of the review of the topic. The included studies had small sample sizes, used short treatment and follow-up periods, and were of relatively low quality overall, which made it problematic to form generalizations and conclusions. No firm conclusions could be drawn based on the existing literature on the methods used. On the other hand, this result emphasized the need for RCTs on CPI in particular.
In study II, the planned number of participants based on power analysis was not achieved in 2 years and the results should therefore be interpreted with caution. VRS as a pain assessment method might be feasible in elderly patients or those with dementia and cognitive impairments. However, VRS may not be sufficiently sensitive to detect changes in pain and therefore has been seldom used in pain studies. A more accurate means of assessing pain in the situation where the patient is not able to use NRS or VAS could be the PAINAD scale. Cognitive impairment in elderly patients may cause difficulties in the assessment of postoperative pain and may bias the results. All patients received a 10-ml bolus of ropivacaine 7.5 mg/ml in both catheters at the end of surgery. However, the effectiveness of this method was previously investigated only in observational studies and one very small RCT and thus the evidence supporting it was very weak. The fact that two catheters were placed in one study also makes it impossible to determine which catheter was

effective. On the basis of previous studies on wound catheters, the wound catheter in addition to a perineural catheter seems unnecessary and is a source of bias in this study.

In study III, all operations from different surgical specialties were pooled for the evaluation of preoperative risk factors. Investigating the risk factors in a heterogenous population of mixed surgical procedures could bias the results. This is based on the fact that thoracic surgery and abdominal surgery are known to be associated with complex postoperative pain (Yang et al. 2019). Preoperative pain, pain catastrophizing, and sleeping quality were not recorded. According to prior studies, these factors (especially preoperative pain) are strong predictors for postoperative pain.

The study design in study IV was exceptional. A questionnaire for the risk evaluation of postoperative pain was constructed based on a prior study (Pan et al. 2013). However, this questionnaire had not been tested in this patient population to stratify patients based on risk of acute postoperative pain. The questionnaire was used for the first time in this study and the only question that predicted acute postoperative pain was the question concerning anxiety. The other four questions did not have predictive value in this study. Therefore, it is doubtful that the study succeeded in its first aim, which was targeting an adjuvant pregabalin to patients with a higher risk for postoperative pain. The fact that the majority of patients had only mild pain after laparoscopic cholecystectomy also made detection of differences between groups challenging.

6.7 STRENGTHS OF THE STUDY

Although the data extracted for the review (study I) was of low quality, a strength of the study is that it was conducted systematically according to the PRISMA statement (defining the principles for a good systematic review) and the Cochrane Bias Tool (for detecting the possible biases of the studies).

Study II has two clear strengths. The number of participants (N=93) is significant and the study is the largest randomized study conducted on this topic, although the target number of 160 participants was not achieved in 2 years. We succeeded in collecting the planned data in this challenging group of elderly patients with numerous comorbidities, dementia, and often some degree of postoperative delirium from multiple study centers. We were able to execute the study due to the good collaboration between study centers and the work of site principal investigators and study nurses.

The strength of study III is that it described the risk factors of a mixed surgical population and aimed to develop simple preoperative questions assessing the risk that could be used in a preoperative evaluation.

In study IV the most important strength is the new and unique study design and the concept of administering an adjuvant analgesic for patients with a higher risk of pain.

6.8 FUTURE ASPECTS AND CLINICAL IMPLICATIONS

Pain management is challenging after major amputations. A combination of different nerve blocks could provide effective relief. For example, a combination of an ischiatic nerve block and a continuous perineural femoral infusion, or a combination of a continuous perineural ischiatic infusion via a catheter combined with a continuous perineural femoral infusion could be of interest to future studies. Furthermore, the role of potential adjuvants, such as duloxetine and pregabalin, should be studied in this patient group.

Although numerous previous studies have identified various risk factors for postoperative pain and higher analgesic consumption, it remains challenging to use these risk factors as predictive tools in clinical practice and to systematically target pain treatment individually based on these factors. To conduct studies on targeting, a consensus of the significant individual psychological risk factors and a tool for screening at-risk patients are needed. The factors that cause bias to these studies on risk factors also need to be considered, such as pre-existing pain and the assumption that the surgical procedure would diminish pain. A clinical study on risk factors such as age, depression (yes or no), anxiety (VAS 0-100), preoperative expectation of pain (four-item scale), preoperative use of opioids, preoperative use of other analgesics, preoperative pain at the site operated (via NRS), and the existence of chronic pain in a simple questionnaire for use in a preoperative setting should be studied among day-case patients. In addition, there is a need for future studies on risk-factor based targeting of analgesics in postoperative pain management. Targeted studies on duloxetine, amitriptyline, and pregabalin could be conducted after identification of a reliable tool for screening risk factors. In the future, genetic studies on acute pain may also lead to improvements in treatment.

Improving postsurgical pain management could begin at the preoperative phase. In addition to planning postoperative analgesia based on the procedure, this could include identifying high-risk patients and planning pain management individually, considering preoperative adjuvants (such as pregabalin, duloxetine, and local anesthetic techniques) and adjuvants (such as ketamine and i.v. lidocaine) in the perioperative and acute postoperative phase. In high-risk patients, the role of preoperative information on pain and pain management is essential. Psychological interventions among high-risk patients should be studied. Psychological interventions based on online services could also be considered. For clinical use, preoperative risk factor screening should be as effortless as possible with a brief validated questionnaire. A questionnaire should evaluate risk factors that are

functional and predictive. High-risk patients should be followed by APS and provided with an outpatient contact after discharge with a pain specialist to ensure the diagnosis of persistent postoperative pain, proper management of pain, and weaning of opioids.

7 CONCLUSIONS

The following conclusions are based on this study:

1. Based on the systematic review of the current literature, there seems to be minimal data to support current clinical practice of pain management in acute pain after amputation. While epidural analgesia may be effective, the treatment regimens are too heterogenous for firm evaluation and the data quality is low. CPI (continuous sciatic perineural infusion of a local anesthetic) probably decreases acute pain levels after major amputation, but the evidence is limited.

2. A combination of continuous sciatic perineural infusion and a wound infusion of a local anesthetic diminishes average stump pain during the first 5 postoperative days and opioid consumption on the first postoperative day after AKA compared to placebo. This combination did not lead to adverse effects in the elderly patients and did not affect the manifestation of chronic pain after amputation.

3. In a wide range of surgical procedures, the role of individual predictive factors (including the expectation of pain, younger age, and the experience of not receiving adequate information on pain and pain management) is noteworthy and has an effect on postoperative pain levels.

4. The simple preoperative question on anxiety (rated on a scale of 0-10) was positively correlated with postoperative pain, but the whole short five-item questionnaire did not predict higher pain levels. Preoperative pregabalin 150 mg administered to cholecystectomy patients with several risk factors for postoperative pain did not decrease postoperative pain intensity compared to placebo.

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